THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

NOVEMBER, 1959

A CLINICAL INVESTIGATION OF LONG-ACTING ORAL CODEINE ANALGESICS EVALUATED STATISTICALLY

By Leo J. Cass, M.D.

DIRECTOR, HARVARD LAW SCHOOL MEDICAL OFFICE, UNIVERSITY HEALTH SERVICES; CHIEF OF MEDICINE, BROOKS HOSPITAL; VISITING PHYSICIAN, MOUNT AUBURN HOSPITAL, CAMBRIDGE, MASSACHUSETTS

Willem S. Frederik, M.D.

LECTURER, HARVARD SCHOOL OF PUBLIC HEALTH, BOSTON, MASSACHUSETTS; DIRECTOR OF RESEARCH, LIBERTY MUTUAL RESEARCH CENTER, HOPKINTON, MASSACHUSETTS

AND

José Teodoro, M.D.

RESIDENT, LONG ISLAND HOSPITAL, BOSTON, MASSACHUSETTS

Oral codeine is widely used in medicine for the alleviation of moderately acute or chronic pain. Moreover, codeine in combination with aspirin is prescribed more frequently than codeine alone, suggesting the clinical acceptance of aspirin as an effective adjunct to codeine analgesia. It has recently been reported that the analgesic effect of codeine is significantly synergized by 2-methyl-3-orthotolyl-quinazolone in both animals (Becker and Hays[1]) and patients (Cass and Frederik[2]).

The present study was undertaken further to evaluate clinically the synergistic combination of codeine with tuazolone and to determine whether or not aspirin will enhance the analgesic effect of this combination. An integral part of the study involves a comparison of the effectiveness of codeine and tuazolone* as long-acting resin complexes with the nonresinated drugs *per se*. As previously reported (Cass and Frederik[2,3]) it is possible to evaluate statistically both short and long-acting drugs in the same clinical study, provided that the necessary factors are taken into account in the experimental design.

Experimental Design. This study was conducted as a completely blind experiment. The medications were supplied and coded by a pharmaceutical research laboratory.† All medications were put up in identically appearing capsules and packaged in plastic tubes. The tubes were coded S–61 to S–67. The seven medications utilized in this study included a placebo and the following drug compounds:

a. Codeine 30 mg. + tuazolone 20 mg. as resin complexes
b. Codeine 30 mg. + tuazolone 20 mg. as resin complexes + methylatropine 6 mg.

*Tuazole is the registered trade name of the R. J. Strasenburgh Co. for its brand of Tuazolone.

†R. J. Strasenburgh Co., Rochester, New York.

c. Codeine 30 mg. + tuazolone 20 mg. as resin complexes + aspirin 5 gr.
d. Codeine sulfate 40 mg.
e. Codeine sulfate 40 mg. + aspirin 5 gr.
f. Aspirin 5 gr.

Sixty-three patients suffering from moderately intense pain were selected for inclusion in the study. These patients were residents of a large chronic disease hospital.* Of the initial 63 patients, 38 patients completed the entire study without missing a single medication dose or a scheduled observation. The clinical diagnoses for these patients are presented in Table 1. The seven medications were given in randomized sequence to all subjects. Each patient was rotated through each of the medications at weekly intervals. Thus, at the end of 7 weeks, each patient was evaluated on the basis of a one-week clinical trial for each medication. Medications were administered at 7 A.M. and 7 P.M. daily. However no observations were made during the first day of drug administration to obviate any carry-over effect of the previously administered medication. Observations for pain relief were made four times a day: 8 a.m., 11 a.m., 3 p.m., and 7 p.m. A specially designed observation card was used and the amount of pain relief was expressed numerically using a scale from 0–4.

0 = no relief
1 = slight relief
2 = moderate relief
3 = almost complete relief
4 = complete relief of pain

TABLE 1.—DIAGNOSES

Rheumatoid arthritis	7
Hypertrophic arthritis	9
Cancer of prostate	3
Neuritis, peripheral	6
Bursitis	2
Fracture, non-union, femur	2
Gouty arthritis	4
Sciatica	3
Radiculitis	2
	38

Side effects were recorded as spontaneously expressed. No questions as to possible untoward symptoms were voiced. The triple blind technique in which observer, patient, statistician and clinician did not know the identity of the 7 medications was followed throughout. As a precautionary measure, a sealed copy of the code was held by the investigators during the study but was returned to the sponsor unopened at the completion of the project.

The conclusions drawn from this study are based upon observations of 38 patients over a 7-week period. The over-all evaluation of each medication is based upon 912 observations. Since seven medications were evaluated, the total number of observations utilized in the statistical analysis of the data were 6,384.

Evaluation of Results. The first step in the statistical analysis of the collected data was the calculation of the average degree of pain relief or the "effectiveness" of the seven coded medications. The average "effectiveness" of each medication was calculated by adding the numerical values of the observations recorded for all 38 patients and dividing this sum by the total number of observations. The average pain relief values were calculated for the following time periods: (a) for each of the 6 days of observation, (b) for each of the 4 observation hours during the day, and (c) for the total 6-day observation period. These values are tabulated in Table 2.

A simple technique used to compare the clinical effectiveness of several drugs is to rank them on the basis of the patients numerical rating of the response obtained. Since the "overall week" average is an expression of the average 12-hour pain-relieving action for each medication, a ranking of the 6-day averages according to magnitude will place them in an "effect" sequence. The most effective medication will have the highest numerical average and the least effective medication will have the lowest. The ranking of the seven coded drugs is shown in Table 3.

Another useful way of "ranking" is to compare for each patient his week scores for each of the 7 coded drugs

*Long Island Hospital, Boston, Massachusetts.

This will give us an impression of the variability between patients in their response to the various analgesics.

Table 4 gives, for each of the coded drugs, the number of patients who ranked this drug as 1, 2, 3, and so forth. Since it was not possible to evaluate these tabulated data without additional analysis, the "average" ranking of each of the 7 drugs was therefore computed. This was done by multiplying the number of patients (see Table 4) by the rank number, adding these products and dividing the sum by the number of patients. This simple procedure was performed for each of the coded drugs. The results are presented in Table 5.

If all patients agree upon the relative effectiveness of the 7 drugs, the "average" ranking would be identical in value to the ranking. For example, Drug S–67, ranked as #7, had also an "average" ranking of 7; simply because all patients agreed that S–67 was the poorest analgesic. Drug S–62, however, ranked as #1, had only an "average" ranking of 2.18. This deviation from rank 1 is an expression of the lack of unanimity between the patients. A close numerical value of "average" ranking, such as between S–61 (3.76) and S–64 (3.79) suggests strongly that both medications have approximately

TABLE 2.—AVERAGE DEGREE OF PAIN RELIEF CALCULATED FOR 38 PATIENTS

Drug	*Day of Observation*						*Hour of Observation*				*Six Day*
Code	*1*	*2*	*3*	*4*	*5*	*6*	*8 AM*	*11 AM*	*3 PM*	*7 PM*	*Totals*
S–61	1.32	1.66	1.76	1.59	1.70	1.45	.93	1.66	2.02	1.72	1.58
S–62	1.60	1.83	1.93	1.78	1.85	1.70	1.09	2.03	2.17	1.84	1.78
S–63	1.40	1.74	1.58	1.68	1.84	1.57	1.03	1.86	2.01	1.65	1.64
S–64	1.18	1.52	1.48	1.57	1.66	1.51	.91	1.62	1.83	1.59	1.49
S–65	1.12	1.30	1.35	1.32	1.47	1.47	.75	1.54	1.72	1.34	1.34
S–66	1.59	1.74	1.78	1.69	1.86	1.67	1.09	1.95	2.15	1.68	1.72
S–67	.77	.67	.63	.59	.75	.65	.46	.90	.73	.62	.68

TABLE 3.—RANKING OF THE CODED DRUGS, USING THE "WEEK AVERAGE" AS CRITERION

Rank	*Code*	*Week Average*
1	S–62	1.78
2	S–66	1.72
3	S–63	1.64
4	S–61	1.58
5	S–64	1.49
6	S–65	1.34
7	S–67	.68

TABLE 4.—RANKING DISTRIBUTION FOR EACH OF THE CODED DRUGS ACCORDING TO PATIENT PREFERENCE

	Code							
Rank	*S–62*	*S–66*	*S–63*	*S–61*	*S–64*	*S–65*	*S–67*	
1	12	11	5	3	6	1	—	38
2	14	6	5	6	5	2	—	38
3	7	7	11	6	5	2	—	38
4	3	7	11	10	5	2	0	38
5	2	7	5	8	9	7	—	38
6	—	—	1	5	8	24	—	38
7	—	—	—	—	—	—	38	38
	38	38	38	38	38	38	38	

the same overall analgesic effect on the patients.

We finally performed a complete series of t-tests between every possible combination of coded drugs.

TABLE 5.—"AVERAGE" RANKING FOR EACH OF THE CODED DRUGS ACCORDING TO PATIENT PREFERENCE

Rank	*Code*	*Average Ranking*
1	S–62	2.18
2	S–66	2.82
3	S–63	3.24
4	S–61	3.76
5	S–64	3.79
6	S–65	5.21
7	S–67	7.00

Table 6 presents the t-values as found comparing the 8 a.m., 11 a.m., 3 p.m., and 7 p.m. values for each of the coded drugs. The drug codes in this table are placed in the same sequence as given in Table 3.

In Table 7, we substituted the t-value for the P-value in instances of a significant t-value. (N.S. = not significant). A "P" of 5% is considered as the lower limit of significance, whereas a "P" of 1% is highly significant. The "larger value" refers to the larger week average and the "smaller value" to the smaller week average. Only if the drug in the vertical column has a larger week average than the drug in the horizontal column, is a "P" value given. This enables us to make conclusions such as, for example,

1. Drug S–62 has a larger week average than drug S–66, but this difference is *not* significant.
2. Drugs S–61, S–62, S–63, S–64, S–65, and S–66 are all significantly better than S–67. The latter, therefore, is presumably the placebo.

SIDE EFFECTS. Side effects as expressed spontaneously were recorded four times daily using the same record card.

TABLE 6.—THE T-VALUES AS CALCULATED BY COMPARING THE 8 A.M., 11 A.M., 3 P.M., AND 7 P.M. OBSERVATIONS OF EACH POSSIBLE COMBINATION OF DRUGS

Drug Code	*S–62*	*S–66*	*S–63*	*S–61*	*S–64*	*S–65*	*S–67*
S–62	—	1.67	4.95	3.45	5.73	12.37	6.43
S–66	1.67	—	3.80	2.03	3.95	17.32	6.42
S–63	4.95	3.80	—	.87	3.70	36.47	6.48
S–61	3.45	2.03	.87	—	2.28	3.90	4.94
S–64	5.73	3.95	3.70	2.28	—	3.84	5.78
S–65	12.37	17.32	36.47	3.90	3.84	—	4.52
S–67	6.43	6.42	6.48	4.94	5.78	4.52	—

TABLE 7.—THE T-VALUES AS GIVEN IN TABLE 6 ARE SUBSTITUTED FOR THE P-VALUES (ONLY IN CASE OF SIGNIFICANCE)

Larger Value \ *Drug Code*	*S–62*	*S–66*	*S–63*	*S–61*	*S–64*	*S–65*	*S–67*
			Smaller Value				
S–62	—	N.S.	2%	5%	2%	1%	1%
S–66		—	5%	N.S.	5%	1%	1%
S–63			—	N.S.	5%	1%	1%
S–61				—	N.S.	5%	2%
S–64					—	5%	2%
S–65						—	2%
S–67							—

Table 8 summarizes for each coded drug the number of times the indicated symptom was observed during a period of 6 days. It is obvious from the tabulated data that there were no appreciable side effects observed with any of the medications; nor was there any significant overall difference in side effects between any of the individual drugs utilized in the study.

TABLE 8.—SUMMARY OF SIDE EFFECTS

Drug Code	*N*	*V*	*C*	*E*	*D*	*U*	*X*	
S–61	1	0	1	3	5	0	1	11
S–62	1	0	4	3	3	1	2	14
S–63	2	1	5	2	6	0	0	16
S–64	2	2	6	3	3	0	1	17
S–65	2	1	3	3	4	0	2	15
S–66	3	0	5	3	3	0	4	18
S–67	4	1	3	2	7	0	1	18
Total	15	5	27	19	31	1	11	109

Number of times a spontaneously expressed side effect was reported. Number of patients = 38. Maximum possible number of each side effect that could be reported during one week is $4 \times 6 \times 36 = 864$.

N = Nausea
V = Vertigo/dizziness
C = Constipation
E = Excitement
D = Drowsiness
U = Euphoria
X = Dry mouth

At the conclusion of the statistical analysis, the identity of the coded medications was revealed. Drugs coded S–62 and S–66 were rated as the most effective medications utilized in the study. Both of these medications were almost identical in composition:

S–62 = Codeine 30 mg. + tuazolone 20 mg. as resin complexes + aspirin 5 gr.

S–66 = same as S–62 + methylatropine 6 mg.

As was predicted from the statistical analysis, S–67 was the placebo. The poorest analgesic in the study was S–65 which contained aspirin only. Apparently, the aspirin present in compounds S–62 and S–66 contributed to their effectiveness, since S–61, which ranked fourth, was identical to S–62 except that it lacked the aspirin.

Summary. By means of a completely blind clinical study employing 38 patients in a cross-over experiment with 6 different oral analgesics and a placebo it was statistically possible to rank the medications in their order of clinical effectiveness.

This study substantiated an earlier report that a single dose of 30 mg. of codeine combined with 20 mg. of tuazolone as ion-exchange resin complexes provided satisfactory pain suppression for almost 12 hours. Furthermore, the simple addition of aspirin 5 gr. to this compound significantly enhanced the degree of pain relief experienced by a majority of patients in the present study. There were no significant side effects noted.

REFERENCES

1. **Becker, B. A.,** and **Hays, E. E.:** Proc. Soc. Exper. Biol. & Med., **99,** 17, 1958.
2. **Cass, L. J.,** and **Frederik, W. S.:** New England J. Med., **259,** 1108, 1958.
3. Iidem: Ann. Int. Med., **49,** 151, 1958

(Interlingua on page 541)

CYANOSIS, CLUBBING AND ARTERIAL OXYGEN UNSATURATION ASSOCIATED WITH LAENNEC'S CIRRHOSIS*

By Theodore Rodman, M.D.
STAFF PHYSICIAN, CARDIOPULMONARY FUNCTION LABORATORY
VETERANS ADMINISTRATION HOSPITAL
INSTRUCTOR IN MEDICINE, TEMPLE UNIVERSITY SCHOOL OF MEDICINE

J. K. Hurwitz, M.D.
RESIDENT IN INTERNAL MEDICINE, VETERANS ADMINISTRATION HOSPITAL

Bernard H. Pastor, M.D.
CHIEF, CARDIOVASCULAR SECTION, VETERANS ADMINISTRATION HOSPITAL
ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE

AND

Henry P. Close, M.D.
CHIEF, MEDICAL SERVICE, VETERANS ADMINISTRATION HOSPITAL
PROFESSOR OF CLINICAL MEDICINE, TEMPLE UNIVERSITY SCHOOL OF MEDICINE

(From the Department of Medicine and the Cardiopulmonary Division of the Medical Research Laboratory, Veterans Administration Hospital, Philadelphia, Pennsylvania)

The occurrence of cyanosis and clubbing of the fingers in association with hepatic cirrhosis has been recognized since 1884 (Flückiger[3]), most frequently in cases of juvenile cirrhosis and in biliary cirrhosis. Routine postmortem examinations have uniformly failed to demonstrate the presence of either right to left shunts or lung disease to account for the arterial oxygen unsaturation demonstrated during life (Evans[2], Gilbert and Fournier[4]).

We have recently observed an adult with Laennec's cirrhosis, cyanosis, clubbing, arterial oxygen unsaturation and congestive heart failure. Extensive physiologic studies of this patient's cardiopulmonary function revealed the presence of a right-to-left shunt of approximately 40% of the cardiac output. There was no clinical evidence of an intracardiac or pulmonary arteriovenous communication that could be responsible for a large shunt.

Case Report. A 60-year-old white man, who had consumed large quantities of alcohol throughout his adult life, first had a diagnosis of Laennec's cirrhosis and beriberi heart disease made at another hospital in 1956. During the year prior to his admission to the Philadelphia Veterans Administration Hospital in March, 1957, he ate poorly, consumed 25 to 75 ounces of whiskey daily, and lost 50 pounds. He complained of dyspnea and swelling of the ankles, and had noticed a recent increase in the number of spider angiomata on his arms and thorax. He could not remember the onset of cyanosis or phalangeal clubbing.

The patient was emaciated and looked chronically ill. His nail beds and mucous membranes were intensely cyanotic, and the terminal phalanges of the hands and feet were clubbed. There were many spider angiomata on the upper thorax and both arms. The heart rate was 104 per minute and the blood pressure 108/58. There was a blowing systolic murmur at the cardiac apex. The liver was firm, tender and enlarged to 3 finger breadths below the right costal margin. There was pitting edema of the ankles.

Laboratory studies, including a hemogram, urinalysis, serologic test for syphilis, blood

*Presented at the Eastern Pennsylvania Regional Meeting of the American College of Physicians, January 23, 1959, Philadelphia, Pennsylvania.

Fig. 1A.—Chest roentgenogram on May 10, 1957, showing nonspecific increase in the pulmonary reticular pattern and old adhesive pleuritis at the left costophrenic angle. The heart is normal in size.

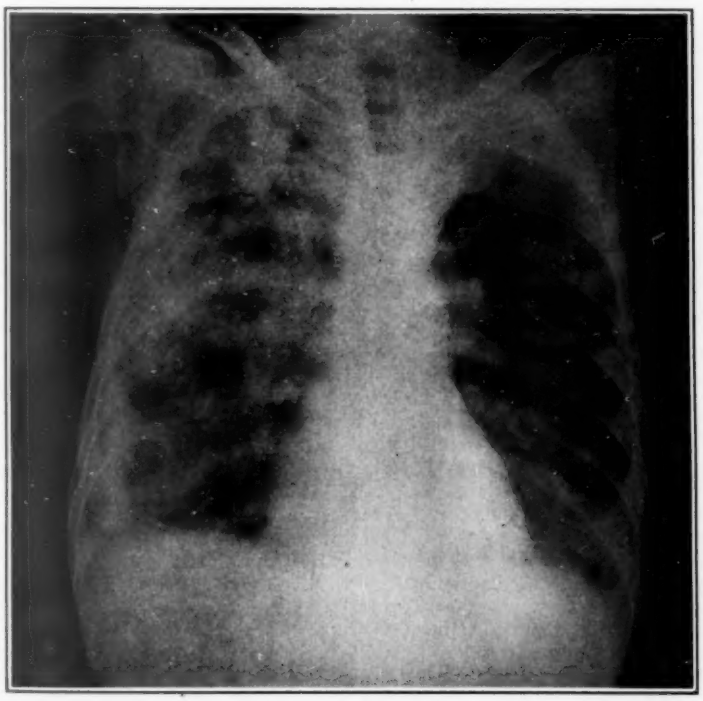


Fig. 1B.—Chest roentgenogram on December 4, 1958, showing extensive pneumonic process with cavitation, most marked on the right.

urea nitrogen, blood sugar, plasma CO_2, serum sodium, potassium, and chloride were normal. Studies of liver function were normal except for a 13.5% Bromsulphalein retention 45 minutes after injection. Smears and cultures of the sputum failed to show acid-fast organisms.

Roentgenograms of the chest (Fig. 1) revealed a nonspecific increase in the pulmonary reticular pattern, but no definite infiltrative process. The heart was not enlarged. There was evidence of old adhesive pleuritis at the left costophrenic angle. Roentgenologic examination of the esophagus, stomach, and duodenum was normal and an electrocardiogram was within normal limits. An angiocardiogram demonstrated no evidence of an intracardiac communication or pulmonary arteriovenous fistula. Pulmonary function studies were first done at this time, and were repeated at intervals during a period of 18 months.

A needle biopsy of the liver revealed extensive fibrous tissue replacement with disruption of the normal hepatic lobular architecture strongly suggestive of highly organized Laennec's cirrhosis.

Biopsy of the right lung was made on July 1, 1957, through a small intercostal incision. It revealed interstitial fibrosis and arteriolosclerosis.

He was treated with a salt restricted high caloric diet, supplemental vitamins, digitalis, and diuretics. There was subjective improvement with disappearance of the edema, and he was discharged in August, 1957.

He was readmitted to the hospital in May, 1958, because of further weight loss and increasing dyspnea. The findings on physical examination, routine laboratory study and roentgenologic examination were unchanged from those of the first hospitalization. An electrocardiogram showed the development of a vertical electrical axis with clockwise rotation. In October a severe pulmonary infection developed and progressed to an extensive bilateral pneumonia with cavitation. Despite antibiotics and supportive therapy the patient died.

A postmortem examination confirmed the antemortem diagnosis of severe Laennec's cirrhosis. The heart was normal in size. No abnormal intracardiac communications were seen. There was a moderate degree of coronary artery atherosclerosis but no gross or histologic evidence of myocardial infarction. Neither ventricle was hypertrophied. The left lung weighed 750 gm., the right, 1400 gm. Because the left lung was less involved by the terminal pneumonitic process, it was preserved intact for injection studies of the pulmonary vasculature. Dissection of the right lung revealed generalized bronchopneumonia and congestion with multiple abscesses in the right upper lobe. Microscopic examination showed multiple areas of suppuration and necrosis with abscess formation. In addition to these acute changes there was interstitial and perialveolar fibrosis with thickening of the alveolar walls and septa. The pulmonary artery and arterioles were sclerotic.

Discussion. In the absence of alveolar hypoventilation, arterial oxygen unsaturation can result from 3 physiologic derangements: 1) increased venous admixture which may be due to either an anatomic right to left shunt or the perfusion of poorly ventilated lung tissue, 2) an alveolar-capillary block with impairment of the diffusion of oxygen into the pulmonary capillary or 3) a decrease in the oxygen-binding capacity of hemoglobin with a shift to the right of the oxyhemoglobin dissociation curve. An evaluation of the cause of the cyanosis in our patient indicates that all 3 potential causes of arterial oxygen unsaturation were present during the period of observation. This is an unusual and possibly a unique situation in clinical pulmonary physiology.

When first studied in May, 1957 (Table 1), the patient's vital capacity was only slightly reduced, the value of 3.14 L. representing 80% of his predicted normal. His maximum breathing capacity was 86 L. per minute. Despite the adequate ventilatory studies and the absence of any evidence of a distribution defect as determined by a normal nitrogen washout, his arterial oxygen saturation was only 72% and his minute ventilation was 14.57 L. as compared with a normal value of less than 6 L. Following the administration of 100% oxygen for 30 minutes the arterial oxygen saturation rose to only 97%. Arterial oxygen unsaturation, however profound, will, when due to lung

disease be fully corrected by prolonged administration of 100% oxygen. The failure to saturate fully is, therefore, pathognomonic of a large anatomic right to left shunt. This was calculated on the basis of the degree of unsaturation to be 37% of the cardiac output. A shunt of the same magnitude was calculated on inhalation of 24.49% oxygen. Analysis of the alveolar-arterial oxygen gradients according to the technique of Riley, Cournand, and Donald[6,7] revealed the presence of a mild alveolar-capillary block, a finding compatible with the interstitial pulmonary fibrosis demonstrated in the lung biopsy and at necropsy. In the absence of the block, however, the resting arterial oxygen saturation would have been only 79%.

When the patient was studied for the second time in May, 1958, the vital capacity was reduced to 2.29 L. (59% of predicted normal) with a corresponding reduction in the maximum breathing capacity to 64 L. per min. (Table 2). The resting arterial oxygen saturation was 70%, and the arterial oxygen saturation on inhalation of 100% oxygen was 92.4%. The magnitude of the right to left shunt had increased to 44% of the cardiac output. The alveolar-capillary block was unchanged. Without it the resting arterial oxygen saturation would have been 74.8% instead of 70%.

In September, 1958, evidence of bronchiolar obstruction and secondary emphysematous changes was present (Table 3). The vital capacity showed a slight further reduction to 2.19 L. and the maximum breathing capacity was reduced to 46 L. per minute. The 3-second vital capacity had decreased

TABLE 1.—PULMONARY FUNCTION STUDIES
MAY, 1957

	Predicted	*Observed*	*% of Normal*
Inspiratory Capacity (L.)	2.89	1.78	62
Expiratory Reserve Volume (L.)	1.00	1.28	128
Vital Capacity (L.)	3.89	3.14	80
3-Second Vital Capacity (% of Total)	>90	94	
Maximum Breathing Capacity (L. per Min.)	86	86	100
Functional Residual Capacity (L.)	3.43	2.89	84
Residual Volume (L.)	2.43	1.61	85
Total Lung Capacity (L.)	6.32	4.67	74
Residual Volume/Total Lung Capacity	.38	.34	
% N_2 in Alveolar Air After 7 Minutes O_2	<2.5	1.5	
ARTERIAL BLOOD			
% O_2 Inspired	*20.89*	*24.49*	*100*
Respiratory Rate Per Minute	21	18	
Minute Ventilations (L.)	14.57	12.34	
Arterial Oxygen Saturation (%)	72.0	79.7	96.7
Whole Blood CO_2 Content (ml./100 ml.)	36.8	38.3	38.5
pCO_2 (mm. Hg)	30	32	33
Arterial pH	7.42	7.41	7.40
Calculated Shunt (%)		38	37

% *Inspired* O_2	*Inspired* pO_2 (*mm. Hg*)	*Alveolar* pO_2 (*mm. Hg*)	*Arterial* pO_2 (*mm. Hg*)	*1–A* Gradient*	*A–A† Gradient*	*Arterial* O_2 *Saturation* %
24.49	174	129	53	45	76	79.7
20.89	148	110	48	38	62	72.0

*Oxygen gradient inspired air to Alveolar air (mm. Hg)
†Oxygen gradient alveolar air to Arterial blood.

TABLE 2.—PULMONARY FUNCTION STUDIES
MAY, 1958

	Predicted	*Observed*	*% of Normal*
Inspiratory Capacity (L.)	2.89	1.23	43
Expiratory Reserve Volume (L.)	1.00	1.05	105
Vital Capacity (L.)	3.89	2.29	59
3-Second Vital Capacity (% of Total)	>90	96	
Maximum Breathing Capacity (L./Min.)	78	64	82
Residual Volume (L.)	2.43	1.43	59
Total Lung Capacity (L.)	6.32	3.99	67
Residual Volume/Total Lung Capacity	.38	.36	
% N_2 in Alveolar Air After 7 Minutes O_2	<2.5	1.2	
Maximum Expiratory Flow Rate (L./Min.)	300	190	65
	ARTERIAL BLOOD		
% O_2 Inspired	*20.83*	*33.95*	*100*
Respiratory Rate Per Minute	23	23	20
Minute Ventilations (L.)	12.97	13.91	10.43
Arterial Oxygen Saturation (%)	70.0	75.3	92.4
Whole Blood CO_2 Content (ml./100 ml.)	43.5	45.1	45.6
pCO_2 (mm. Hg)	33	33	36
Arterial pH	7.45	7.47	7.44
Calculated Shunt (%)		44	44

Percent Inspired O_2	*Inspired pO_2 (mm. Hg)*	*Alveolar pO_2 (mm. Hg)*	*Arterial pO_2 (mm. Hg)*	*1–A* Gradient*	*A–A† Gradient*	*Arterial O_2 Saturation %*
33.95	242	200	50	42	150	75
20.83	149	106	48	43	58	70

*Oxygen gradient inspired air to Alveolar air (mm. Hg)
†Oxygen gradient alveolar air to Arterial blood

TABLE 3.—PULMONARY FUNCTION STUDIES
SEPTEMBER, 1958

	Predicted	*Observed*	*% of Normal*
Inspiratory Capacity (L.)	2.89	.96	33
Expiratory Reserve Volume (L.)	1.00	1.23	123
Vital Capacity (L.)	3.89	2.19	56
3-Second Vital Capacity (% of Total)	>90	81	
Maximum Breathing Capacity (L./Min.)	78	46	59
Residual Volume (L.)	2.43	3.78	156
Total Lung Capacity (L.)	6.32	5.63	89
Residual Volume/Total Lung Capacity	.38	.67	
% N_2 in Alveolar Air After 7 Minutes O_2	<2.5	3.4	
Maximum Expiratory Flow Rate (L./Min.)	300	52	18
Single Breath N_2 (%)	<1.5	2.5	
	ARTERIAL BLOOD		
% O_2 Inspired	*20.76*	*39.48*	*100*
Respiratory Rate Per Minute	25	23	22
Minute Ventilations (L.)	12.27	11.44	11.68
Arterial Oxygen Saturation (%)	63.1	81.9	91.2
Whole Blood CO_2 Content (ml./100 ml.)	45.9	46.2	46.9
pCO_2 (mm. Hg)	33	39	41
Arterial pH	7.48	7.40	7.38
Calculated Shunt (%)		42	42

Percent Inspired O_2	*Inspired pO_2 (mm. Hg)*	*Alveolar pO_2 (mm. Hg)*	*Arterial pO_2 (mm. Hg)*	*1–A* Gradient*	*A–A† Gradient*	*Arterial O_2 Saturation %*
39.48	285	245	62	40	183	81.9
20.76	150	113	39	37	74	63.1

*Oxygen gradient inspired air to Alveolar air (mm. Hg)
†Oxygen gradient alveolar air to Arterial blood.

to 81% and the maximum expiratory flow rate was only 52 L. per minute, indicating severe airway obstruction. Inspired gases were unevenly distributed as indicated by an alveolar nitrogen concentration of 3.4% after breathing oxygen for 7 minutes and an alveolar nitrogen concentration change of 2.5% on a "single breath nitrogen test." The residual volume had increased to 3.78 L. Resting arterial oxygen saturation had dropped to 63.1%. The size of the shunt was unchanged (42%), but the alveolar-capillary block had increased. Without it, the resting arterial oxygen saturation would have been 76.3% instead of 62.1%. These studies suggested progression of the primary lung disease and correlated well with the clinical status of the patient.

By simultaneously determining the *in vivo* oxygen tension by the bubble equilibration technique of Riley, Proemmel, and Franke[8], the oxygen saturation, and the blood pH during the inhalation of several different concentrations of oxygen, the *in vivo* oxyhemoglobin dissociation curve was plotted (Fig. 2). It is significantly displaced to the right. This shift is teleologically sound in the presence of moderate arterial oxygen unsaturation because of the peculiar shape of the oxyhemoglobin dissociation curve (A flat upper limb and a steeply descending mid portion). The reduced affinity of hemoglobin for oxygen permits the tissues to extract more oxygen in the capillary bed with little decrease in the oxygen saturation of the arterial blood. Although Keys and Snell, using an *in vitro* tonometric technique, demonstrated such a rightward displacement of the dissociation curve in patients with hepatic cirrhosis[5], we have been unable to demonstrate any displacementment in 16 other patients with

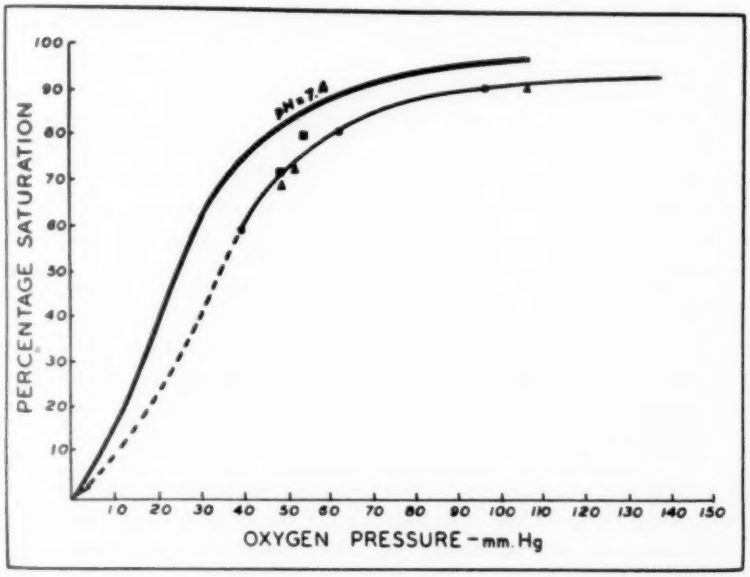


Fig. 2.—The *in vivo* oxyhemoglobin dissociation curve plotted for comparison with the standard curve of Dill at pH 7.4. Note displacement downward and to the right indicating a reduced affinity of hemoglobin for oxygen.

severe Laennec's cirrhosis using the *in vivo* technique mentioned above. We have, however, demonstrated a shift to the right in a few patients with arterial oxygen unsaturation secondary to primary lung disease. The mechanism by which the decreased oxygen saturation produces a reduction in the affinity of hemoglobin for oxygen is obscure.

The cause of the cyanosis occasionally observed in patients with cirrhosis has been the subject of some speculation. Recently 2 possible explanations have been suggested.

Rydell and Hoffbauer[9] studied a 22-year-old patient with post-necrotic cirrhosis, cyanosis and clubbing. Gross and histologic examination of the lungs revealed no abnormality except pulmonary venous distention, but they demonstrated the presence of multiple small arteriovenous fistulas by injecting the pulmonary arterial tree with a plastic (vinyl acetate). The vascular channels of the A–V communications were very small, approximately the size of the A–V communications involved in cutaneous spider angiomata.

This possibility was investigated after the death of our patient. The pulmonary vessels and tracheobronchial tree of the left lung, which was less involved by the terminal infectious process, were injected with a plastic material by Dr. Averill Liebow. No arteriovenous communications were demonstrated and we have been unable to confirm the findings of Rydell and Hoffbauer. Multiple small pulmonary arteriovenous fistulas have been demonstrated only in young patients with hepatic cirrhosis in whom there may be an associated congenital malformation. It seems likely that in adult cirrhotics some other physiologic mechanism is responsible for the arterial oxygen unsaturation when present.

Another explanation for the cyanosis has been suggested by Calebresi and Abelmann[1], who demonstrated communications in postmortem specimens between the portal venous and pulmonary venous circulation through the paraesophageal, mediastinal, hemiazygous and azygous systems. A plastic mass injected under pressure into the portal vein was recovered in the pulmonary veins and left atrium. A high portal venous pressure may certainly exist in advanced cirrhosis, and account for the shunting of blood through these collateral channels.

Indirect evidence in support of this theory rather than that of the pulmonary arteriovenous shunts analogous to spider angiomata has recently been obtained in another patient with portal hypertension but without liver disease, in whom arterial oxygen unsaturation has been demonstrated due to venous admixture. The findings in this patient suggest that it is the portal hypertension rather than hepatic disease *per se* which is responsible for the increased venous admixture.

Summary. Extensive pulmonary function studies were done on a 60-year-old man with the clinical syndrome of hepatic cirrhosis, cyanosis, and phalangeal clubbing. Severe arterial oxygen unsaturation was present. A right to left shunt of approximately 40% of the cardiac output was demonstrated by physiologic studies to be the primary factor responsible for the arterial oxygen unsaturation. No anatomic lesion was found clinically or by postmortem examination to account for the shunt.

The presence of multiple minute pulmonary arterio-venous fistulas has been suggested as the etiology of this syndrome. No such fistulas were demonstrated by plastic injection of one lung in this patient. It is suggested that porto-pulmonary venous communications by way of the mediastinal and bronchial network may be responsible for the shunt.

ACKNOWLEDGMENT: The authors would like to express their appreciation to Dr. Averill Liebow, Professor of Pathology, Yale University School of Medicine, for kindly performing the injection of the necropsy specimen.

REFERENCES

1. **Calabresi, P.**, and **Abelmann, W. H.**: J. Clin. Invest., **36**, 1257, 1957.
2. **Evans, P. R.** (for **Sheldon, W.**): Proc. Roy Soc. Med., **30**, 406, 1937.
3. **Flückiger, M.**: Wien. med. Wchnschr., **34**, 1457, 1884.
4. **Gilbert, A.**, and **Fournier, F.**: Compt. rend. Soc. Biol., 10th ser., **2**, 419, 1895.
5. **Keys, A.**, and **Snell, A. M.**: J. Clin. Invest., **17**, 59, 1938.
6. **Riley, R. L.**, and **Cournand, A.**: J. Appl. Physiol., **4**, 77, 1951.
7. **Riley, R. L.**, **Cournand, A.**, and **Donald, K. W.**: Ibid., **4**, 102, 1951.
8. **Riley, R. L.**, **Proemmel, D. D.**, and **Franke, R. E.**: J. Biol. Chem., **161**, 621, 1945.
9. **Rydell, R.**, and **Hoffbauer, F. W.**: Am. J. Med., **21**, 450, 1956.

SUMMARIO IN INTERLINGUA

Cyanosis, Digitos Hippocratic, e Nonsaturation Oxygenic Arterial in Association con Cirrhosis de Laennec

Extense studios de function pulmonar esseva effectuate in un homine de 60 annos de etate con le syndrome clinic de cirrhosis hepatic, phalanges hippocratic, e cyanosis. Sever grados de nonsaturation oxygenic arterial esseva presente. Un shunt dextero-sinistre de circa 40% del rendimento cardiac esseva demonstrate per studios physiologic e interpretate como le principal factor responsabile pro le nonsaturation oxygenic arterial. Nulle lesion anatomic capace a explicar le shunt esseva trovate clinica- o necropticamente.

Le presentia de multiple minuscule fistulas arterio-venose in le pulmones ha essite proponite como etiologia de iste syndrome. Nulle tal fistulas esseva demonstrate per injection de plastico in un del pulmones de iste patiente. Es formulate le these que un communication venose porto-pulmonar, via le retes mediastinal e bronchial, esseva possibilemente responsabile pro le shunt.

SUMMARIO IN INTERLINGUA

(See page 529 for original article)

Un Investigation Clinic de Oral Analgesicos Codeinic, Evalutate Statisticamente

Super le base de un completemente "occulte" studio clinic, utilisante 38 patientes in un experimento de "permutation" de septe gruppos de subjectos, septe medicationes (sex differente analgesicos oral e un placebo), e septe periodos de administration, il esseva possibile alinear le medicationes in le ordine de lor efficacia clinic.

Iste studio corrobora le previe reporto que un dose unic de 30 mg de codeina in combination con 20 mg de tuazolona in le forma de complexos a resina de excambio de iones provide un adequate suppression de dolores pro periodos de quasi 12 horas. In plus, le simple addition de 5 g de aspirina a ille composito potentiava significativemente le grado del alleviamento de dolor experientiate per le majoritate del patientes in le presente studio. Nulle significative effectos lateral esseva notate.

THE EFFECT OF PREDNISONE AND 6-METHYL-PREDNISOLONE ON MERCURIAL DIURESIS IN PATIENTS WITH REFRACTORY CARDIAC EDEMA

By János P. Radó, M.D.

Gyula Blumenfeld, M.D.

and

Sarolta Hammer, M.D.

(From the Isotopic Department and Metabolic Unit, János Hospital, Budapest, Hungary)

In patients with refractory cardiac edema the return of sensitivity to mercurial diuretics often breaks the vicious circle of severe circulatory failure and delays fatal outcome. In recent years, since the discovery of Schemm and Camara[46], we have successfully employed ACTH treatment for resistant congestive heart failure[16,40,41]. After the introduction of prednisone and prednisolone into clinical medicine, steroid therapy for cardiac edema became particularly popular (Bickel[5], Cattan and Vesin[10], Fabre[15], Ginoulhiac[19], Gutner *et al.*[22], Mertz[31], Mickerson and Swale[32], Muller *et al.*[33], Newman[35], Page and Lavender[36], Riederer[43], Riemer[44], Ballabio *et al.*[2], Scalabrino and Curtarelli[45], Villa, Ballabio and Sala[48], Wolff and Koczorek[49]).

The great advantage of prednisone was the relatively slight mineralocorticoid (sodium-retaining and potassium-wasting) activity as compared with ACTH, cortisone and hydrocortisone in doses with the same glucocorticoid, anti-inflammatory and pituitary corticotropin suppressive potency (DiRaimondo and Forsham[14], Nabarro, Stewart and Walker[34]).

Certain recently discovered synthetic steroids, practically without sodium-retaining activity promise to be even more useful in the treatment of cardiac edema; in the present study we have dealt with effects of 6-methyl-prednisolone, one of the compounds mentioned above.

The exact mechanism of steroid diuresis, in spite of extensive investigations, is not quite clear, as yet. Some increase in glomerular filtration rate due to the administration of certain corticosteroids has been shown in normal subjects (Bonati *et al.*[6], Dingman *et al.*[13], Froesch *et al.*[18], Raisz *et al.*[42]), and especially in patients suffering from nephrosis (Goodman and Baxter[20]) and decompensated portal cirrhosis (Cattan and Vesin[10]). Nevertheless, the suppressive effect of corticosteroids on the secondary hyperaldosteronism (Bartter *et al.*[4], Buchborn, Koczorek and Wolff[8], Fabre[15], Gross[21], Liddle[29], Muller *et al.*[33], Wolff and Koczorek[49]), the inhibition of hypothalamic centers governing the antidiuretic hormone secretion (Dingman *et al.*[13]) as well as the increase in free water clearance (Raisz *et al.*[42]), "an action on the renal tubules which is independent of antidiuretic activity"[28], emphasize the importance of various tubular mechanisms in the "paradoxical" diuretic actions of glucocorticoids. There are, however, other theories for the explanation of the "mysterious" diuretic effects: a direct myocardial action mentioned al-

ready by Schemm and Camara[46], correction of the adrenocortical deficiency or of the increased production of thyrotropic hormone, or both, reported by Mickerson and Swale[32]. The presence of variable urine electrolyte patterns during the administration of ACTH[24,46], led Schemm and his colleagues to the conclusion that more than one mechanism may be responsible for the favorable clinical and diuretic effects. The relatively weak diuretic effect of prednisone administered alone to patients included in this study together with the prompt relief of mercury-resistance suggest different mechanisms for actions causing a cessation of refractoriness and increasing "spontaneous diuresis."

The purpose of the present work is to study the effect of prednisone and 6-methyl-prednisolone on the glomerulotubular functions during mercurial diuresis in cases with refractory cardiac edema.

Materials and Methods. Patients with congestive heart failure (due to rheumatic, hypertensive and arteriosclerotic heart disease) were divided into two groups: 1) mercury-sensitive control patients and 2) refractory patients. The criteria for grouping were the same as in our previous work[41]. Six patients were classified as belonging to the first group and 4 patients to the second. The average age in the two groups was 54 and 62, respectively. All of these patients were studied daily, until an optimal condition had been reached. The data obtained in the sensitive and resistant groups (in the latter before and during prednisone) were compared in 4-day periods: the "Novurit day" was preceded by one and followed by two "control days." In the statistical analysis the data of several 4-day periods were compared by the t test for the mean of unique samples.

The clearance studies were made by double catheterization between 9 and 12 a.m. on control-days and from 12 to 3 p.m. on the Novurit-days. Novurit (and in one case Esidron) were given in doses of 2 ml. intravenously, between 8 and 8.30 a.m. The urine chloride concentration and the quantity excreted (output) were also determined during the clearance periods mentioned above, and their values were expressed in mEq. per L. and mEq. per min., respectively. Blood samples were taken every morning at 8 a.m. on the control days and at 2 p.m. on the Novurit days for serum sodium and serum chloride determinations. Chemical methods were the same as in reference[41]. The sodium concentration was determined by standard internal flame photometer (data only in part reported here, see Fig. 5).

Using all clearance values obtained (including those in oliguria) we were able to confirm Chesley's early findings[11] and those of Balint of more recent date[1], showing a correlation between the urine flow and the endogen creatinine clearance in oliguria (data not presented). The investigations of Philips *et al.*[37] and Balint *et al.*[1] seem to indicate that such correlation is, physiologically, an obviously erroneous one (the exact explanation is beyond the scope of this study). Therefore the clearance values were accepted only when the diuresis was at least 0.60 ml. per min. or higher.

In the sensitive group Novurit was the only diuretic used; in the refractory group adjuvant drugs (ammonium chloride, Diamox, and others) were discontinued during the test period. One case (L.T.) is not included in the statistical studies since, owing to the patient's critical condition, we had to start with steroid without withdrawing adjuvants.

Prednisone was given in the usual clinical dosage (30 to 40 mg. daily, orally in divided doses; 6 methyl-prednisolone was administered to patient L.T. in daily doses of 12 mg.).

Results. In response to Novurit, body weight decreased in 48 hours by an average of 2.98 kg. in the sensitive group (hereafter designated as "S") as compared to 0.40 kg. in the refractory ("R") group. On the other hand, during treatment with prednisone (hereafter designated "Pr.") the decrease amounted to 2.50 kg. (Table 1, Figs. 1 and 5).

In response to Novurit the urine flow was 4.05 ml. per min. in "S" and 1.80 ml. per min. in "R". Under "Pr." it rose to 5.11 ml. per min. (Table 1, Figs. 1 and 5).

In response to Novurit the urine chloride output was 0.6195 mEq. per min. in "S" as compared to 0.1962 mEq.

TABLE 1.—THE EFFECT OF PREDNISONE TREATMENT ON MERCURIAL DIURESIS IN REFRACTORY CARDIAC PATIENTS IN COMPARISON WITH A WELL-RESPONDING, (SENSITIVE) CONTROL GROUP.

	*Control (sensitive) Group.**				*Refractory Group*							
					Before prednisone†				*During prednisone‡*			
	1 day before	*6 hours after*	*1 day after*	*2 days after*	*1 day before*	*6 hours after*	*1 day after*	*2 days after*	*1 day before*	*6 hours after*	*1 day after*	*2 days after*
	NOVURIT				NOVURIT				NOVURIT			
Change in body weight (Kg.)	−0.27	——	−2.53	−0.45	+0.16	——	−0.52	+0.92	0.00	——	−2.95	+0.45
Urine flow (ml./min.)	0.49	4.05	0.65	0.45	0.38	1.80	0.60	0.37	0.45	5.11	0.56	0.39
Chloride excretion (mEq./min.)	0.0485	0.6195	0.0623	0.0378	0.0057	0.1962	0.0459	0.0171	0.0304	0.7072	0.0459	0.0194
Serum chloride concentration (mEq./L.)	99.1	94.3	89.6	92.4	91.2	96.2	96.8	96.0	97.7	95.6	90.7	94.2
Urine chloride concentration (mEq./L.)	92	155	82	83	16	109	88	41	64	145	79	42

*The average of 15 "four day periods" in 6 patients.
†The average of 6 "four day periods" in 3 patients.
‡The average of 7 "four day periods" in 3 patients.

per min. in "R". Under "Pr." it rose to 0.7072 mEq. per min. (Table 1, Figs. 1 and 5). The data for other days are shown in Table 1.

The serum chloride concentration decreased in "S" by 9.6 ± 1.6 mEq. per L. Standard deviation (s.d.): 5.1; $t = 6.0$; $P<0.001$ (very highly significant) (Fig. 3 and Table 1).

The serum chloride concentration did not decrease in "R" (Table 1, Fig. 3) but under "Pr." it decreased by

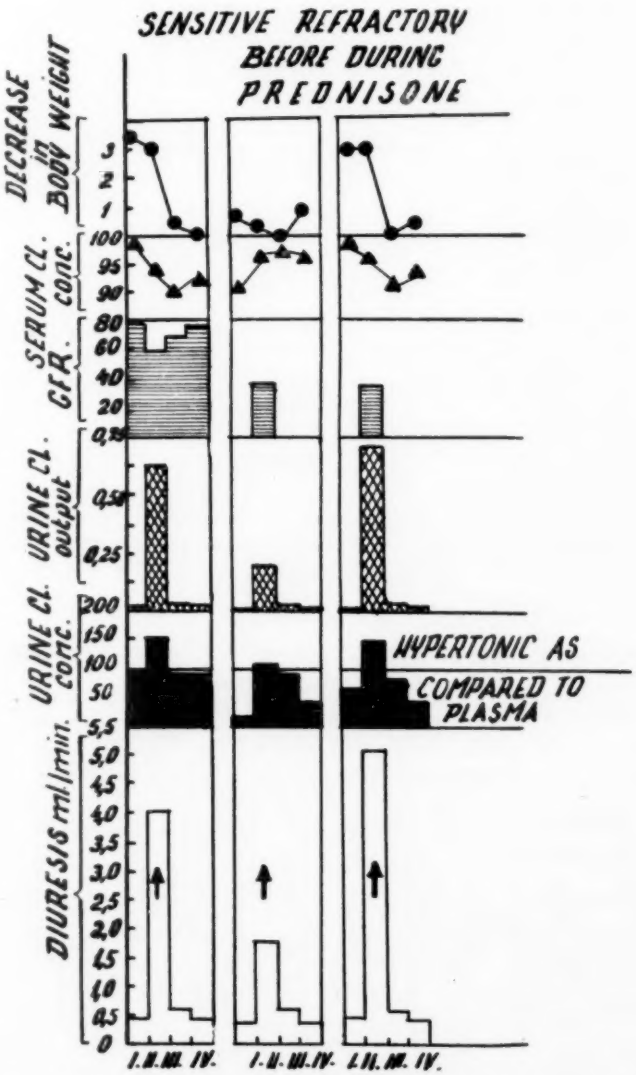


Fig. 1.—The effect of a mercurial diuretic (Novurit) in two groups of patients with congestive heart failure. Note the reappearance of "mercury-type" diuresis in the prednisone-treated refractory group, common in mercury sensitive patients (I, II, III and IV stand for days before, during, 1 and 2 days after Novurit).

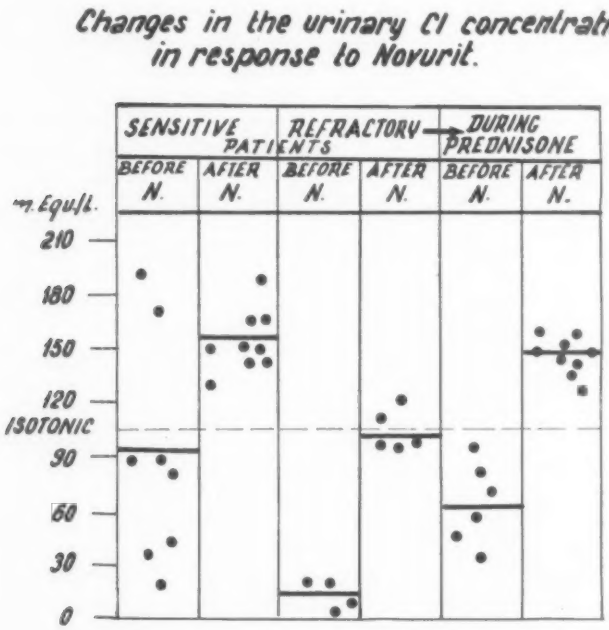


Fig. 2.—Note: 1) the convergence of the variable (high and low) urinary chloride concentration to the characteristic value of 150 mEq./L. during mercurial diuresis in sensitive patients; 2) the excessive hypochloruria, hardly responding to mercury during the refractory state; 3) the comparable hypertonic urine chloride concentration during mercurial diuresis in sensitive and prednisone-treated refractory patients.

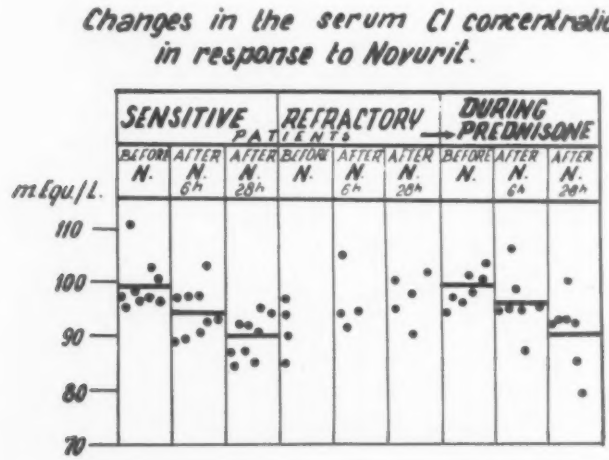


Fig. 3.—Note the decrease in serum chloride concentration during mercurial diuresis in sensitive and prednisone-treated refractory patients. During refractory state there is no decrease.

8.1 ± 2.6 mEq. per L. S.D.: 6.75; t = 3.18; P<0.002 (significant).

The values mentioned above represent the change in serum chloride concentration during the first 28 hours of of mercurial diuresis. (In Figs. 1, 3 and 5 the 6-hour and 52-hour change can be also seen.)

Endogenous creatinine clearance was 74 ml. per minute in "S" and only 54 ml. per min, in "R". (These are uncorrected values; considering the average dry weight for "S", 44 kg., and for "R", 58 kg., the effective difference between the two groups is much greater.)

In response to Novurit the decrease in "S" averaged 17.8 ± 6.7 ml. per min. S.D. = 21.5; t = 2.66; P<0.005 (significant) (Tables 1 and 2 and Fig. 4). In "R" the decrease was 17.0 ± 1.5 ml. per min.

The Novurit-day values are included

TABLE 2.—GLOMERULAR FILTRATION RATE CHANGES DURING AND AFTER MERCURIAL DIURESIS IN THE NOVURIT-SENSITIVE GROUP.*

	1 day before N	*6 hours after* O	*1 day after* V	*2 days after* U	*3 days† after* R I	*4 days‡ after* T
Urine flow‡ (ml./min.)	0.72	4.05	0.97	1.07	0.85	0.84
Endogeneous creatinine clearance (ml./min.)	78	59	68	76	74	80

*Average of 15 "four day periods" in 6 patients.
†Only in a part of the periods
‡Clearance values during oliguria were excluded.

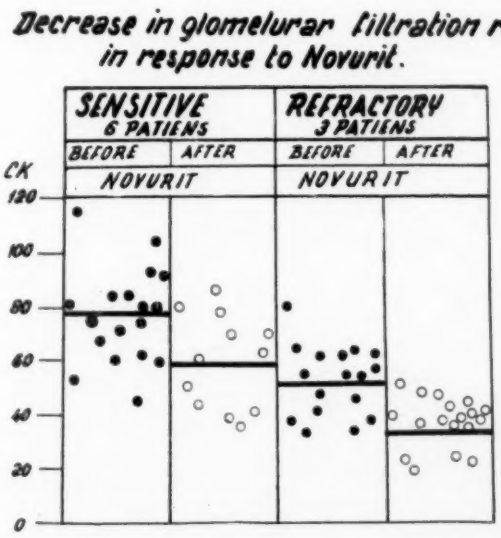


Fig. 4.—Note the decrease in endogenous creatinine clearance during the peak of mercurial diuresis in both groups of patients with congestive heart failure. In refractory patients the clearance values are lower than in the sensitive ones.

in the statistical analysis for the 3 patients of the refractory group, before and after prednisone: 43, 20, 48 ml. per min. and 42, 25, 46 ml. per min. respectively. (Each figure represents the average clearance value of several determinations.) (Figs. 1 and 5.)

The reduction in glomerular filtration rate in response to mercurial diuretics has been previously reported by Pitts and his colleagues[26,39] and was also confirmed by Hársing[23].

Case Report of a Patient Treated with 6-Methyl-Prednisolone. L.T., a 65-year-old woman, a housewife, was hospitalized on January 28, 1959, because of advanced congestive heart failure, refractory to different mercurial diuretics. The failure was due to rheumatic valvular and hypertensive heart disease associated with a marked pulmonary emphysema and a cardiac cirrhosis of the liver.

HISTORY. The patient's heart disease had been discovered some 30 years ago. At that time she had only a slight dyspnea. In the past decade she had needed diuretic treatment and at the end of this period was being maintained on Novurit, 2 ml. every 4 or 5 days. Since December, 1956, she had been hospitalized three times, each time for sudden worsening of her cardiac condition. Her response to Novurit had always been good up to November, 1958; therefore she was included in the "sensitive group" of this study. In 1957, her glomerular filtration rate was 65 ml. per min. during mercurial diuresis, as measured by the endogenous creatinine clearance. At the end of 1958 she failed to respond to Novurit and Esidron. Hyperchloremic acidosis obtained by the administration of ammonium chloride and acetazolamide failed to restore the mercury-sensitivity. The patient became critically ill. The situation seemed to be hopeless to the hospital staff, nurses and relatives. On February 3, 1959, the patient was placed on 6-methyl-prednisolone treatment. In order to prevent infection and thromboembolism she was given streptomycin and, in divided doses intravenously, heparin.

CLINICAL COURSE. There was a dramatic response to the 6-methyl-prednisolone treatment. Within 48 hours she became less dyspneic and cyanotic without any decrease in edema (measured clinically, through recording daily the changes in body weight). On the fourth day of steroid therapy she was given Esidron with a good response. After 4 more days the mercurial diuretic was repeated with dramatic relief of the condition, but 24 hours after the injection the patient complained of severe, sudden chest pain and dyspnea. She again became cyanotic and a pleural friction rub was heard. The diagnosis of pulmonary infarction was made. The therapy had not been changed, including continued administration of the anticoagulant. The further course was uneventful; the patient recovered cardiac compensation. Her body weight decreased from 50 to 36 kg., and she was entirely edema-free. She was discharged on March 1, 1959. In the next 2 months she was placed on prednisone (10 mg. daily) besides her usual dietary-cardiac-diuretic treatment. Her edema returned only partially, the increase in dyspnea was slight and immediately relieved after the administration of the mercurial diuretic. As the sodium restriction at home was comparable with that in the hospital, the reason for return of edema is not quite clear; it is suspected that the change from 6-methyl-prednisolone to prednisone may be a responsible factor. Nevertheless, the general condition of the patient is quite satisfactory and to this date there has been no decrease in mercury sensitivity (for details see Fig. 5).

Discussion. In our patients responding well to Novurit, the advantageous clinical effects of mercurial diuretics were accompanied by marked serum and urine electrolyte changes (in accordance with our previous studies[41]). These changes could be used as laboratory signs of a satisfactory response type congestive heart failure.

In sensitive patients during mercurial diuresis the urine chloride concentration was hypertonic (150 mEq. per L.) when compared with the serum (100 mEq. per L.). As a consequence, in the latter the chloride concentration dropped markedly (from 100 mEq. per L. to 90 mEq. per L.) (Figs. 1–3).

By the decrease in glomerular filtration rate during the peak of mercurial diuresis we were able to confirm the fact that only the inhibition of chloride reabsorption in the renal tubules may be responsible for the electrolyte

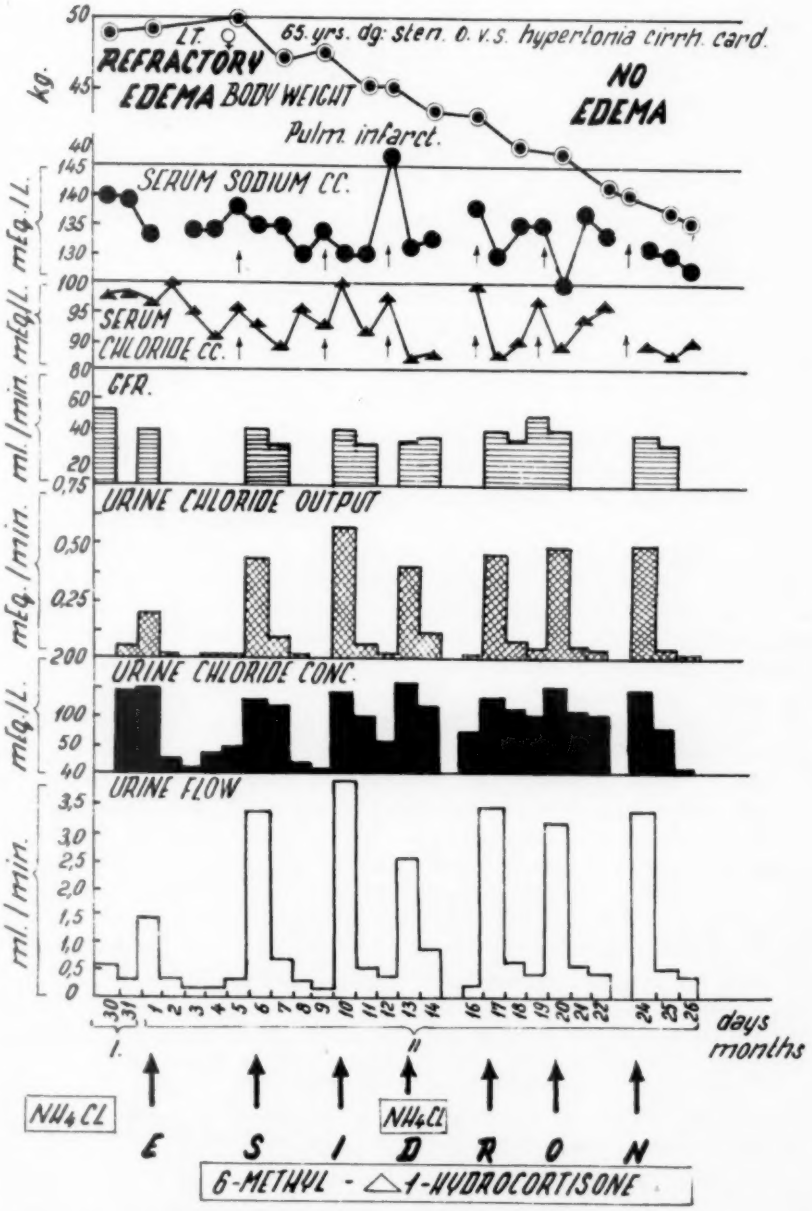


Fig. 5.—The effect of 6-methyl-prednisolone in a patient with refractory cardiac edema. Note the prompt return of mercury-sensitivity. A rapid decrease in body weight (edema) can be seen in spite of the low glomerular filtration rate, dropping further in the course of treatment and despite the decreasing tendencies in serum electrolytes.

changes observed in sensitive patients (Figs. 1, 4 and 5).

In response to prednisone and 6-methyl-prednisolone, patients formerly in refractory state, exhibited again the clinical and aforementioned "laboratory criteria" of good mercury effect (Figs. 1, 3 and 5). The reappearance of the mercury-type diuresis (with the characteristic electrolyte changes in serum and urine) was interpreted as a sign of restored sensitivity of renal tubules to mercury, disproving that under steroid treatment the increased mercurial diuresis is due to a simple summation of actions of the "diuretics" (mercury and prednisone) used. A more direct bit of evidence supporting this contention was that, during peak mercurial diuresis, the same clearance values were obtained before and during steroid treatment (Figs. 1 and 5). These data seem to indicate that prednisone and 6-methyl-prednisolone may restore sensitivity to mercury by a purely tubular mechanism.

Our "tubular hypothesis" is in harmony with data published in recent years (see Laragh's report[27]). It has been shown that edema may be formed even without changes in renal hemodynamics, or even when glomerular filtration is increasing (Barger *et al.*[3], Davis and Howell[12], Frieden, Rice and Elisberg[17], Pitts[38]). On the other hand, edema may be absent in some cases of heart failure, although glomerular filtration is decreased (Hollander and Judson[25]). It is well known that edemas may be drained off even without any increase in glomerular filtration (Briggs *et al.*[7], Sinclair-Smith *et al.*[47], Radó and Blumenfeld[41]). Nevertheless, we believe that the relief of a refractory condition by a "tubular method" is not necessarily in controversy with some early data of the representatives of the "forward failure theory"corroborated by a careful, recent statistical study (Buchborn *et al.*[9]).

The exact mode of action of the mercurial diuretic on the tubular cell has not been fully elucidated. There are some controversies as regards the fate of such compounds in the renal tubules (Kessler, Lozano and Pitts[26], Levy, Weiner and Mudge[30]). Our knowledge is fragmentary about the effect of prednisone on the tubular metabolic processes governing the fate of mercury compounds.

Summary. The authors observed restoration of mercury-sensitivity in patients with refractory cardiac edema as a consequence of steroid treatment with prednisone and 6-methyl-prednisolone.

The relief of refractoriness was accompanied by the reappearance of certain laboratory criteria, characteristic of the good mercury response, which are absent in the refractory state.

The results of clearance studies seem to indicate that prednisone and 6-methyl-prednisolone, probably by a purely tubular mechanism, can restore mercury-sensitiveness in patients with refractory cardiac edema.

ACKNOWLEDGMENT. We are greatly indebted to Dr. Hubert C. Peltier and the Upjohn Company for a generous supply of 6-methyl-prednisolone, marketed as Medrol.

REFERENCES

1. **Bálint, P., Fekete, A., Hajdu, A., László, K.,** and **Pintér, G.:** Acta physiol. Hungarica, **6**, 81, 1954 and Kisérletes Orvostudomány, **5**, 352, 1953 (Hungarian text).
2. **Ballabio, C. B., Amira, A., Cirla, E.,** and **Sala, G.:** Reumatismo, **7**, 113, 1955.
3. **Barger, A. C., Ross R. S., Price, H. L., Wilson, G. M.,** and **Brooks, L.:** Proc. 19th Internat. Physiol. Congress, p. 188, 1953.
4. **Bartter, F. C., Liddle, G. W., Duncan, L. E., Barber, J. K.,** and **DeLea, C. J.:** J. Clin. Invest., **36**, 767, 1958.

5. **Bickel, G.:** Arch. Mal. Coeur, **49**, 651, 1956.
6. **Bonati, B., Bergamini, A., Rancati, G. B.,** and **Tedeschi, G.:** Minerva méd., **53**, 26, 1955.
7. **Briggs, B. P., Fowell, D. M., Hamilton, W. F., Remington, J. W., Wheeler, N. C., Winslow, J.:** J. Clin. Invest., **27**, 810, 1948.
8. **Buchborn, E., Koczorek, K. R.,** and **Wolff, H. P.:** Klin. Wchnschr., **35**, 452, 1957.
9. Iidem: Ibid., **37**, 71, 1959.
10. **Cattan, R.,** and **Vesin, P.:** Semain Hop. Paris, **32**, 712, 1956, and **33**, 76, 1957.
11. **Chesley, L. C.:** J. Clin. Invest., **16**, 653, 1937; **17**, 119, 1938; and **17**, 591, 1938.
12. **Davis, J. O.,** and **Howell, D. S.:** Circulation Res., **1**, 260, 1953.
13. **Dingman, J. F., Finkenstaedt, J. T., Laidlaw, J. C., Renold, A. E., Jenkins, D., Merrill, J. P.,** and **Thorn, G. W.:** Metabolism, **7**, 608, 1958.
14. **DiRaimondo, V. C.,** and **Forsham, P. H.:** Ibid., **7**, 5, 1958.
15. **Fabre, J.:** Schweiz. med. Wchnschr., **87**, 470, 1957.
16. **Fodor, I., Blumenfeld, G.,** and **Radó, J.:** Orvosi Hetilap, **96**, 349, 1955. (Kongress-centralblatt f. Inn. Med., **171**, 353, 1956.)
17. **Frieden, J., Rice, L.,** and **Elisberg, E. I.:** Am. J. Physiol., **168**, 93, 1952.
18. **Froesch, E. R., Winegrad, A. I., Renold, A. E.,** and **Thorn, G. W.:** J. Clin. Invest., **37**, 524, 1958.
19. **Ginoulhiac, R.:** Minerva méd., **48**, 315, 1957.
20. **Goodman, H. C.,** and **Baxter, J. H.:** Metabolism, **7**, 40, 1958.
21. **Gross, F.:** Klin. Wchnschr., **34**, 929, 1956.
22. **Gutner, L. B., Moses, J. B., Dann, S.,** and **Kupperman, H. S.:** Am. J. Med. Sci., **234**, 281, 1957.
23. **Hársing, L.:** Kandidatusi dissertatió, Budapest, 1956 (Hungarian text) and Acta phys. Acad. Sci. Hung., **12**, 363, 1957.
24. **Heidorn, G. H.,** and **Schemm, F. R.:** Am. J. Med. Sci., **229**, 621, 1955.
25. **Hollander, W.,** and **Judson, W. E.:** J. Clin. Invest., **35**, 970, 1956.
26. **Kessler, R. H., Lozano, R.,** and **Pitts, R. F.:** J. Clin. Invest., **36**, 656, 1957.
27. **Laragh, J. H.:** Am. J. Med., **21**, 423, 1956.
28. Leading Article: Brit. Med. J., **1**, 910, 1959.
29. **Liddle, G. W.:** Science, **126**, 1016, 1957.
30. **Levy, J., Weiner, J. M.,** and **Mudge, G. H.:** J. Clin. Invest., **37**, 1016, 1958.
31. **Mertz, D. P.:** Verh. Deutsch. Ges. Inn. Med., **63**, 508, 1957.
32. **Mickerson, J. N.,** and **Swale, J.:** Brit. Med. J., **1**, 876, 1959.
33. **Muller, A. F., Riondel, A. M., Manning, E. L.,** and **Mach, R. S.:** Schweiz. med. Wchnschr., **86**, 1335, 1956 and **86**, 1362, 1956.
34. **Nabarro, J. D. N., Stewart, J. S.,** and **Walker, G.:** Lancet, **2**, 993, 1955.
35. **Newman, D. A.:** New York State J. Med., **59**, 625, 1959.
36. **Page, R. G.,** and **Lavender, A. R.:** J. Clin. Invest., **35**, 728, 1956.
37. **Philips, R. A., Dole, V. P., Hamilton, P. B., Emerson, K., Archibald, R. M.,** and **Van Slyke, D. D.:** Am. J. Physiol., **145**, 314, 1946.
38. **Pitts, R. F.:** Am. J. Med., **24**, 745, 1958.
39. **Pitts, R. F.,** and **Duggan, J. J.:** J. Clin. Invest., **29**, 372, 1950.
40. **Radó, J.,** and **Blumenfeld, G.:** Orvosi Hetilap, **98**, 408, 1957 (Hungarian text).
41. Iidem: Acta med. Scandinav., **160**, 15, 1958.
42. **Raisz, L. G., McNeely, W. F., Saxon, L.,** and **Rosenbaum, J. D.:** J. Clin. Invest., **36**, 767, 1957.
43. **Riederer, J.:** Artzliche Forsch., **11**, 3, 1957.
44. **Riemer, A. D.:** Bull. Johns Hopkins Hosp., **98**, 445, 1956.
45. **Scalabrino, R.,** and **Curtarelli, G.:** Minerva méd., **46**, 1431, 1955.
46. **Schemm, F. R.,** and **Camara, A. A.:** Circulation, **11**, 702, 1955.
47. **Sinclair-Smith, B., Kattus, A. A., Genest, J.,** and **Newman, E. V.:** Bull. Johns Hopkins Hosp., **84**, 369, 1949.
48. **Villa, L., Ballabio, C. B.,** and **Sala, G.:** Rev. Rhumat., **22**, 413, 1955.
49. **Wolff, H. P.,** and **Koczorek, K. R.:** Deutsch. med. Wchnschr., **83**, 250, 1958.

(Interlingua on page 583)

RESULTS OF LACTIC DEHYDROGENASE DETERMINATIONS IN BENIGN AND MALIGNANT EFFUSIONS

By Mercedes Vincente de Torregrosa, Ph.D.
attending in pathology, san juan city hospital
associate professor in clinical pathology, school of medicine
university of puerto rico, san juan, puerto rico

Many workers have become interested in the changes of specific enzymes associated with various pathological conditions. The serum transaminases (glutamic oxalacetic and pyruvic) and lactic dehydrogenase have been more widely studied.

In this communication we intend to report lactic dehydrogenase levels obtained in the serum and effusions of a group of patients suffering from benign and malignant conditions.

Material and Methods. The simple colorimetric method described by Cabaud and Wroblewski[2] has been employed; normal serum values range from 200 to 680 units.

The sera and fluids studied were obtained from patients hospitalized in the San Juan City Hospital; data from a few private patients were also included in the series to be reported.

Results and Discussion. High values for serum lactic dehydrogenase have been found in a variety of clinical conditions. This is readily understandable as the enzyme is widely distributed in the human body and alterations of tissues rich in lactic dehydrogenase may result in increased serum values.

Increases in serum lactic dehydrogenase which occur in malignant conditions have been attributed to the release of the enzyme from malignant cells and being correlated to the size of the tumor mass or masses (West and Zimmerman[4]); by contrast, increases in serum glutamic oxalacetic transaminase in patients with carcinomatosis are usually related to the presence of metastases to organs containing high levels of the enzyme, such as the liver and the heart. In the fluid medium bathing malignant cells in tissue cultures large amounts of lactic dehydrogenase are obtained (Wroblewski[5]).

Furthermore, Wroblewski[5] believes that benign and malignant effusions can be differentiated by measuring their content of lactic dehydrogenase and comparing it to the serum values. The authors found, in benign conditions, a lower lactic dehydrogenase in the effusions than in the serum, in contrast to higher lactic dehydrogenase effusion values in patients suffering from malignant conditions.

The results of lactic dehydrogenase determinations in the sera and effusions of 20 patients suffering from benign conditions are found in Fig. 1. Papanicolaou stains of the sediment of the pleural and ascitic fluids were negative for malignant cells. Ten patients with liver cirrhosis (Laennec's), 4 with cardiac cirrhosis, and 2 with collagen disease were studied. In every instance the serum lactic dehydrogenase value was higher than that of the effusion, confirming the non-malignant nature of the condition. Among 3 patients suffering from pulmonary tuberculosis with pleural effusion, one had a higher value for lactic dehydrogenase in the effusion than in the serum. The patient had no clinical evidence of a malignant condition.

Figure 2 presents the data on patients with various types of malignancy. The fluids in every instance yielded a positive cytology. High serum values were found in many of the patients

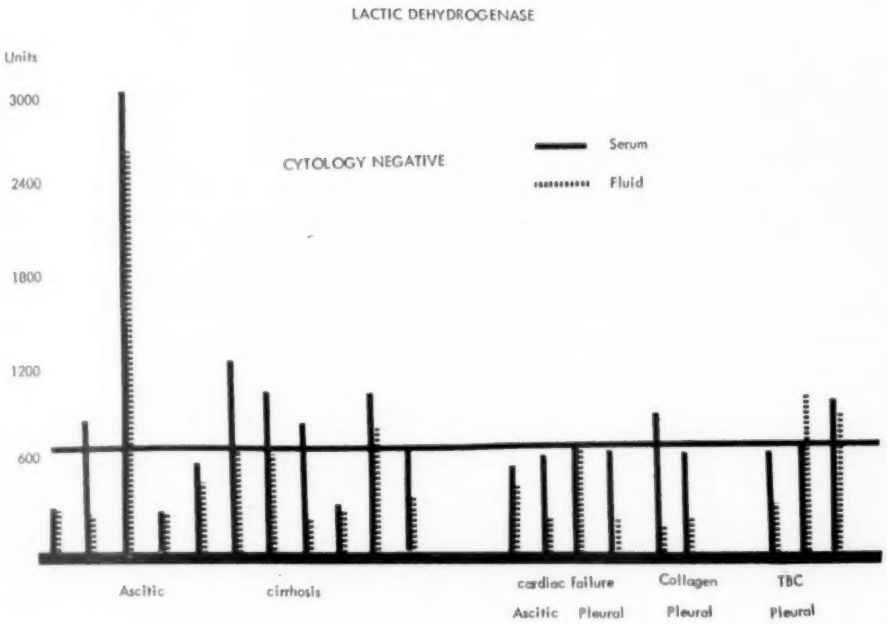


Fig. 1.—Serum and effusion lactic dehydrogenase values in patients with miscellaneous benign conditions.

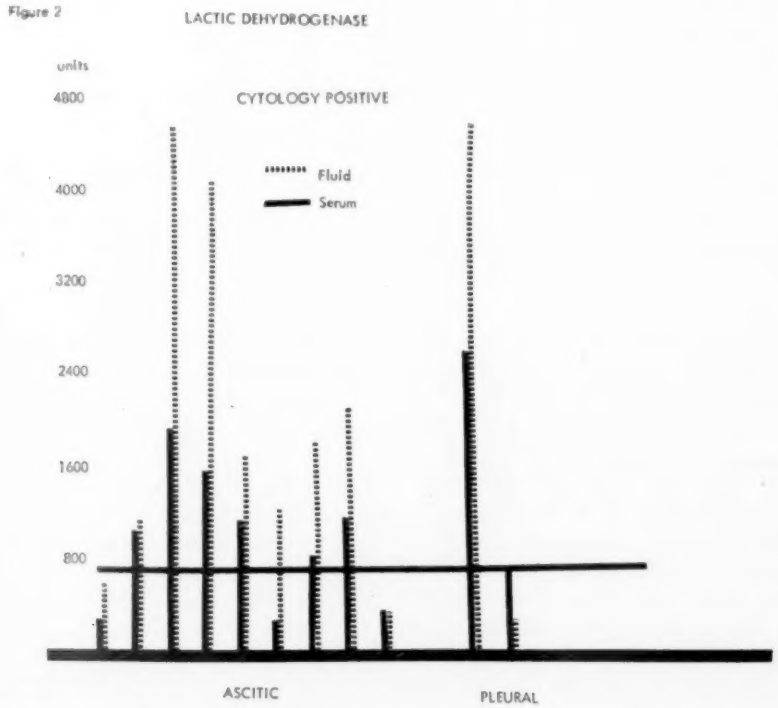


Fig. 2.—Comparison of lactic dehydrogenase activity of serum and serous effusions in patients with neoplastic disease.

thus confirming the findings of others (Bierman *et al.*[1], Hill and Levi[3]). Lactic dehydrogenase values in the effusions were higher than the serum values in 9 out of 11 patients. The 2 patients with a lower effusion lactic dehydrogenase were diagnosed respectively at laparotomy as adenocarcinoma of the pancreas with metastases; and metastatic carcinomatosis, primary site unknown. Numerous malignant cells were found in the effusions of both patients. They had received no treatment.

Individual diagnostic problems will be discussed separately. In Fig. 3 we find the data on a 36-year-old woman in whom the operative diagnosis was pseudomucinous adenocarcinoma of the ovary; postoperatively she received Roentgen-ray therapy. Two months later the patient had accumulated abdominal fluid which had a negative cytology and a chylous appearance. The amount of lactic dehydrogenase in the serum was about the same as that of the fluid on 2 different occasions. At laparotomy no metastases were found. The accumulation of fluid was interpreted as due to reaction to irradiation therapy; the patient is doing well.

In Fig. 4 are illustrated the findings in J.J., a 71-year-old woman whose final diagnosis was adenocarcinoma of the breast. A pleural fluid obtained October 23, 1956, yielded a positive cytology; the patient was given stilbestrol 5 mg. t.i.d., for over one year. Fluid accumulated again and a tap performed December 11, 1957, yielded an effusion with negative cytology and a lactic dehydrogenase value of 271 units; the serum lactic dehydrogenase was 297 units. Biopsy of the breast (April 28, 1958) was reported as adenocarcinoma. The lactic dehydrogenase findings in this patient may be related to the results of treatment; some

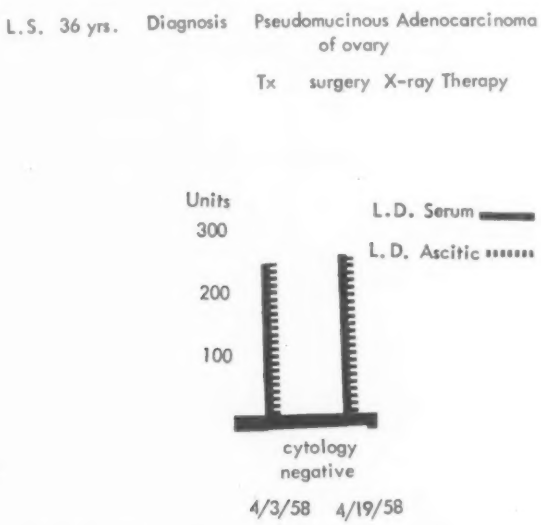


Fig. 3.—Ascites associated with reaction to Roentgen-ray therapy; comparison of lactic dehydrogenase values in serum and peritoneal fluids. x Clinical data on this patient (L.S.) obtained from Dr. Raul Marcial, Liga Contra el Cancer.

authors believe that treatment alters the production of lactic dehydrogenase by malignant cells (Wroblewski[5]).

The results of our studies in R.R., a 41-year-old woman patient with a final diagnosis of linitis plastica are found in Fig. 5. Abdominal fluid obtained June 20, 1958, showed a negative cytology, low specific gravity and low lactive dehydrogenase value. Paracentesis performed July 14, 1958, however, revealed fluid with a high specific gravity, positive cytology and high lactic dehydrogenase as compared to the serum value. This case demonstrates the importance of repeated determinations in selected cases.

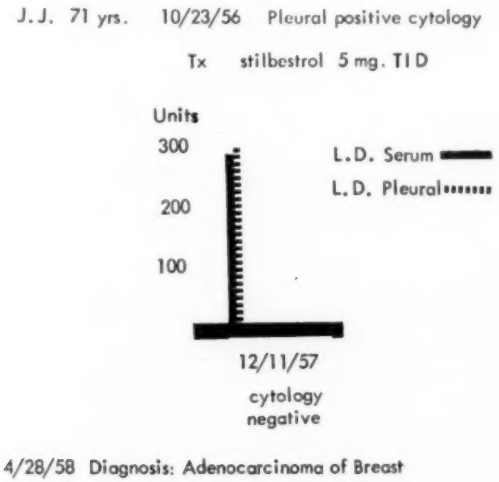


Fig. 4.—Enzymatic activity (L.D.) of serum and pleural fluid of a patient with carcinomatosis after treatment with stilbestrol.

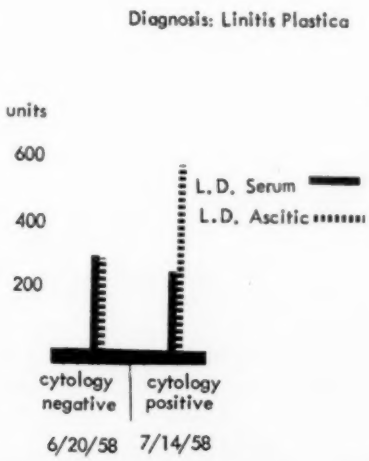


Fig. 5.—Comparative lactic dehydrogenase determinations in serum and peritoneal fluid of a patient with neoplastic disease.

Summary and Conclusions. 1. The amount of lactic dehydrogenase found in the sera and effusions of patients suffering from various clinical conditions have been compared.

2. In patients with untreated carcinomatosis a higher value for lactic dehydrogenase in the effusion was found in the great majority of them.

3. The pleural and ascitic fluids obtained from 19 cases which included cirrhosis, cardiac failure, collagen diseases and tuberculosis had a low content of lactic dehydrogenase. One patient with active pulmonary tuberculosis had a higher lactic dehydrogenase in the pleural effusion than in the serum.

4. Comparative studies of serum and effusion lactic dehydrogenase seem to be of great help in the differentiation of benign and malignant conditions.

REFERENCES

1. **Bierman, H. R., Hill, R., Emory, E., Rinhardt, L.,** and **Samuels, A.:** Proc. Am. Assn. Cancer Res., **2**, 5, 1955.
2. **Cabaud, P. G.,** and **Wroblewski, F.:** Am. J. Clin. Path., **30**, 234, 1958.
3. **Hill, B. R.,** and **Levi, C.:** Cancer Res., **14**, 513, 1954.
4. **West, M. W.,** and **Zimmerman, H. J.:** A.M.A. Arch. Int. Med., **49**, 102, 1958.
5. **Wroblewski, F.:** Am. J. Med. Sci., **234**, 301, 1957.

SUMMARIO IN INTERLINGUA

Resultatos de Determinationes de Dishydrogenase Lactic in Effusiones Benigne e Maligne

1. Le quantitates de dishydrogenase lactic trovate in le seros e le effusiones de patientes suffrente de varie conditiones clinic esseva comparate.

2. In patientes con nontractate carcinomatosis, un plus alte nivello de dishydrogenase lactic esseva incontrate in le effusiones in le majoritate del casos.

3. Le liquidos pleural e ascitic obtenite in un serie de 19 patientes, incluse casos de cirrhosis, disfallimento cardiac, morbo de collageno, e tuberculose, habeva un basse contento de dishydrogenase lactic. Un patiente con active tuberculose pulmonar habeva un plus alte concentration de dishydrogenase lactic in le effusion pleural que in le sero.

4. Studios comparative del contento de dishydrogenase lactic in seros e effusiones pare esser de grande adjuta in le differentiation inter conditiones benigne e maligne.

CONGENITAL DEFORMITY OF THE ATRIOVENTRICULAR VALVE LEAFLETS SIMULATING RHEUMATIC MITRAL INSUFFICIENCY*

By Sidney Friedman, M.D.
ASSISTANT PROFESSOR IN PEDIATRICS, UNIVERSITY OF PENNSYLVANIA

Katherine A. Hallidie-Smith, M.R.C.S., L.R.C.P., D.Ch.
RESEARCH FELLOW IN PEDIATRIC CARDIOLOGY
THE CHILDREN'S HOSPITAL OF PHILADELPHIA

AND

T. N. Harris, M.D.
PROFESSOR OF IMMUNOLOGY IN PEDIATRICS, UNIVERSITY OF PENNSYLVANIA

(From the Rheumatic Fever Research Laboratory and the Department of Cardiology of The Children's Hospital of Philadelphia, the Rheumatic Fever Clinic of the Philadelphia General Hospital and the Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania)

The vast majority of patients with significant cardiac murmurs in childhood have either congenital or rheumatic heart disease (Friedman and Wells[4]). The differentiation of these two etiologic varieties of heart disease in the pediatric age group is usually not difficult on the basis of auscultation alone. Thus, the systolic murmur generally found in rheumatic heart disease, that due to mitral insufficiency, is high-pitched and blowing in quality and of maximal intensity at the apex. In contrast, the systolic murmurs associated with most congenital cardiac anomalies are of lower pitch, have a harsh or rough quality and are of maximal intensity along the left sternal border. Nevertheless, 4 children were recently encountered among a group of approximately 350 children enrolled in a rheumatic fever clinic in whom an apical systolic murmur characteristic of mitral valvular insufficiency was present as a result of a congenital deformity of the atrioventricular valve leaflets rather than of rheumatic heart disease. The congenital etiology of the lesion giving rise to cardiac murmurs in these children was first suspected after critical review of the roentgenograms and electrocardiograms. By cardiac catheterization the diagnosis was subsequently proved to be a partial form of persistent common atrioventricular canal. This report presents clinical and laboratory findings in these 4 children and oscillographic and spectrographic tracings of the cardiac murmurs found in this condition.

CLINICAL OBSERVATIONS. A summary of the salient clinical features observed in the 4 patients under consideration is included in Table 1. A positive family history of rheumatic fever was present in only one case; in no instance were the noncardiac manifestations of rheumatic fever a part of the past medical history. A cardiac murmur was discovered incidentally in all cases; in 2 patients this observation was made initially during infancy. The history of

*This study was supported in part by grants from the National Heart Institute of the U.S. Public Health Service, the Pennsylvania Heart Association and the Heart Association of Southeastern Pennsylvania.

frequent respiratory tract infections in 2 of the 4 children may be related to their excessive pulmonary blood flow.

On physical examination the height and weight of only 2 of the children were found to be below average. Overt cyanosis, hypertension and palpable precordial thrills were absent in all

In routine laboratory studies no significant degree of anemia was detected. One patient who was seen for the first time shortly after a streptococcal respiratory tract infection had a rapid erythrocyte sedimentation rate and elevated antistreptococcal antibody titers.

TABLE 1.—CLINICAL FINDINGS IN 4 CHILDREN WITH ATRIOVENTRICULAR VALVULAR INSUFFICIENCY OF CONGENITAL ORIGIN

History	*Case 1*	*Case 2*	*Case 3*	*Case 4*
Birth Order	2nd of 6	6th of 6	6th of 6	1st of 2
Birth Weight	3305 gm.	2430 gm.	2185 gm.	2740 gm.
Family History of Rheumatic Fever	Positive	Negative	Negative	Negative
Age Cardiac Lesion First Noted	1 year	6 years	6 years	1½ years
Occasion for P.E. At Time Lesion First Noted	Intercurrent Infection	Intercurrent Infection	Routine School Examination	Routine Examination by Family Physician
Past Medical History	Frequent URI's	Negative	Negative	Frequent URI's
Cardiovascular Symptoms	None	None	None	Easy Fatigability
Age Congenital Origin Established	7½ years	6½ years	6 years	4 years
Physical Examination				
Height Percentile	3	10	50	50
Weight Percentile	3	10	50	50
Blood Pressure	110/80	110/70	100/50	90/60
Thrills	None	None	None	None
Cardiac Murmurs				
Apical Systolic	+	+	+	+
Basal Systolic	+	+	+	+
Apical Diastolic	+	+	+	+
2nd Pulmonic Sound	Widely Reduplicated	Widely Reduplicated	Widely Reduplicated	Widely Reduplicated
Triple Rhythm	+	+	+	+
Initial Laboratory Data				
Hemoglobin	12.7 gm. %	11.7 gm. %	13.4 gm. %	12.9 gm. %
Corrected ESR	7 mm./hr.	42 mm./hr.	<5 mm./hr.	8 mm./hr.

cases. In addition to a high-pitched blowing apical systolic murmur, there was, in each instance, a mid-diastolic murmur at the apex or a short distance to the right of the apex. A low-pitched basal systolic murmur was also present in all 4 children. Wide reduplication of the second heart sound was present in the second left intercostal space in all instances; at the apex a triple rhythm was uniformly present.

Figure 1 contains the initial roentgenogram, in the anterior-posterior view, of each patient. Slight cardiac enlargement was present in 3 cases and moderate enlargement in one (Case 4). Rounding and prominence of the right heart border in the anterior-posterior view was present in all cases, indicating some degree of right atrial enlargement. In 3 instances the aorta was considered smaller than normal in size;

the pulmonary artery was dilated in all 4 cases. The peripheral pulmonary vascular markings were consistently exaggerated. Left atrial enlargement could not be demonstrated with a barium swallow in any of the 4 children.

The electrocardiographic findings in these 4 patients are shown in Table 2. abnormalities were noted. A representative tracing (Case 2) is shown in Fig. 2.

A summary of the findings at the time of cardiac catheterization is presented in Table 3. In each instance a significant arteriovenous shunt was demonstrable at either the atrial or ventricular level. In 3 patients a significant shunt of arterialized blood was found to be entering the right atrium. In the remaining case, possibly because of inadequate sampling low in the right atrium, only a ventricular shunt was demonstrated. Severe pulmonary hypertension or pulmonary stenosis was not present in any case. Definite arterial unsaturation was found only in

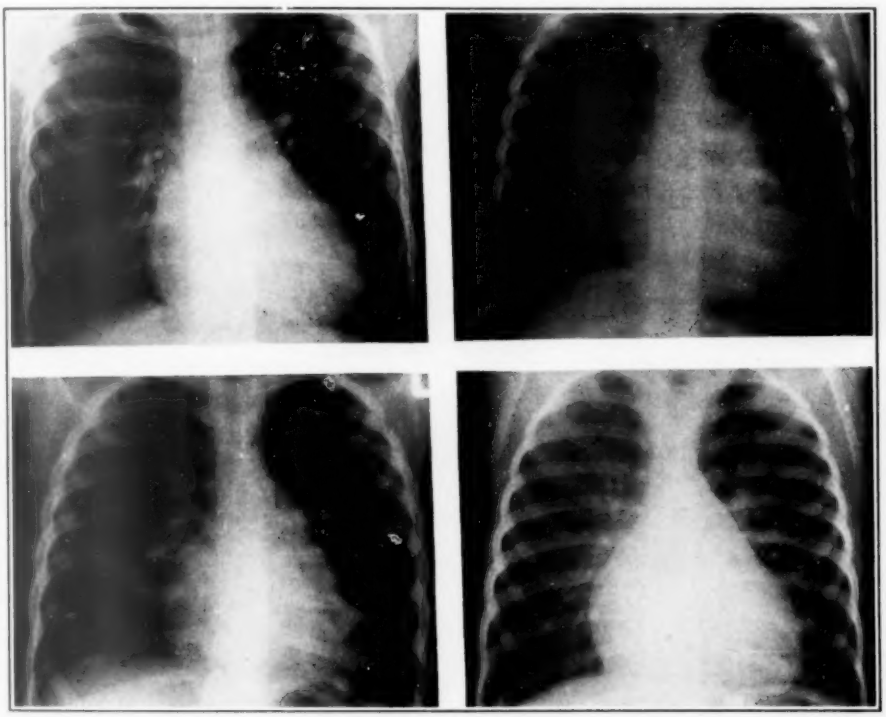


Fig. 1.—Initial roentgenograms obtained in the AP view from each patient demonstrate (1) slight to moderate cardiac enlargement (2) a prominent, rounded right cardiac border indicative of right atrial enlargement (3) prominent pulmonary artery segment and small aortic shadow (4) accentuated peripheral pulmonary vascular markings.

Prolongation of the PR interval was present in each instance. Intraventricular conduction was not delayed. In each instance, left axis deviation was present and unipolar-lead records obtained from the precordium yielded evidence of right ventricular or biventricular hypertrophy. Peaking of P_2 was present in 2 instances. No T-wave

TABLE 2.—ELECTROCARDIOGRAPHIC FINDINGS IN 4 CHILDREN WITH ATRIOVENTRICULAR VALVE DEFORMITY OF CONGENITAL ORIGIN

	1 (D.P.)	*2 (J.P.)*	*3 (R.M.)*	*4 (M.F.)*
Cardiac rate per minute	120	95	100	120
Duration of P–R interval	0.16	0.21	0.18	0.16
Duration of QRS complex in lead II	0.10	0.10	0.09	0.09
Axis Deviation	Left (−62°)	Left (−55°)	Left (−65°)	Left (−75°)
R/S Ratio in V_1	1.3	3.3	0.5	1.4
R/S Ratio in V_5	1.3	1.5	2.3	3.1
QRS configuration in AVR	Diphasic	Diphasic	Diphasic	Predominant R
P waves	P_1 intermittently diphasic	P_2 slightly peaked	Normal	P_2 slightly peaked
T waves	Normal	Normal	Normal	Normal

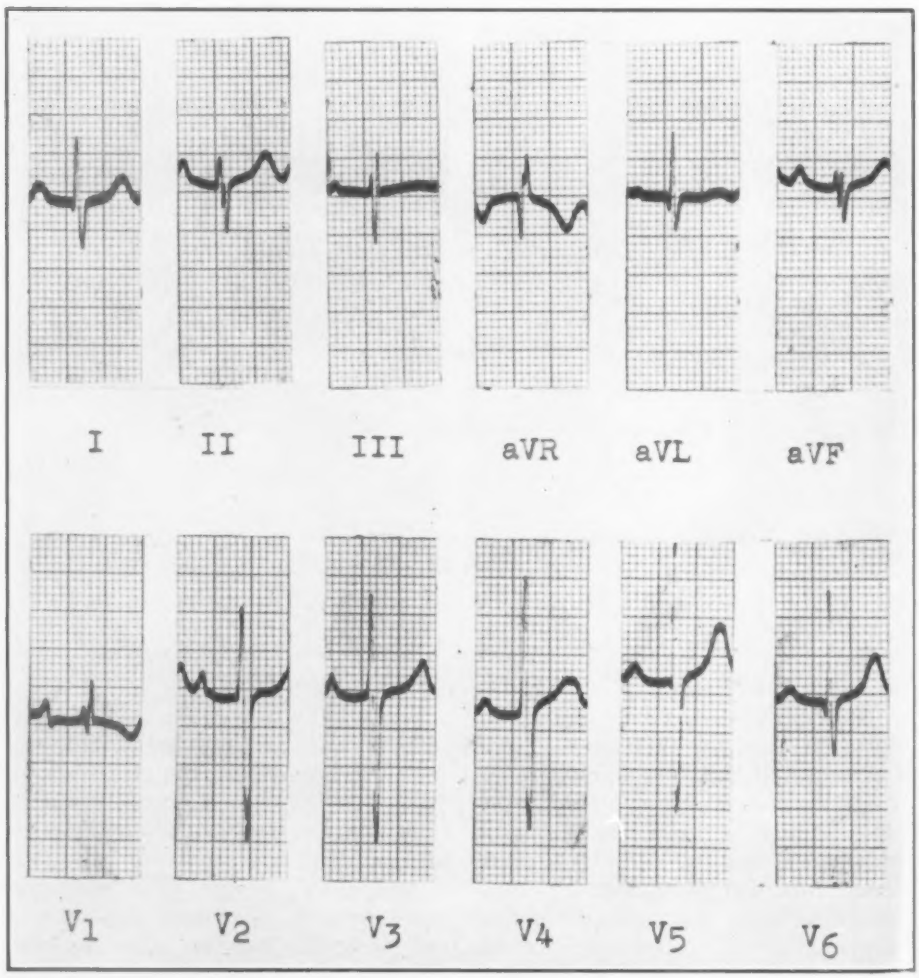


Fig. 2.—Electrocardiogram recorded from 6½-year-old girl (Case 2) reveals left axis deviation in the limb leads and evidence of right ventricular hypertrophy in the precordial leads.

TABLE 3.—CARDIAC CATHETERIZATION FINDINGS IN 4 CHILDREN WITH CONGENITAL DEFORMITY OF ATRIOVENTRICULAR VALVE LEAFLETS SIMULATING RHEUMATIC MITRAL INSUFFICIENCY

	Case 1 (D.P.)			*Case 2 (J.P.)*			*Case 3 (R.M.)*			*Case 4 (M.F.)*		
	Oxygen content	*% Saturation*	*Pressure*	*Oxygen content*	*% Saturation*	*Pressure*	*Oxygen content*	*% Saturation*	*Pressure*	*Oxygen content*	*% Saturation*	*Pressure*
Superior Vena Cava	10.0	65.5		8.6	59.1		13.7	79.0		11.5	66.5	
Right Atrium	11.6	76.8	10/6	10.4	72.5	8/2	16.1	94.0	5/2	14.5	83.7	12/4
Low Right Ventricle	13.0	84.9	40/2	12.1	84.5	38/0	16.3	99.0	25/2			36/6
High Right Ventricle	13.8	91.1		12.6	83.2							
Right Pulmonary Artery	11.8	76.3	36/16	11.9	83.0	35/12				13.3	75.7	20/5
Left Atrium							17.0	96.0				
Left Ventricle							16.6	94.0	98/5			
Brachial Artery	14.4	96.9	100/65	14.3	97.6	110/70			110/70	14.6	83.8	90/60

case 4. Comparable findings on cardiac catheterization have been observed in patients with complete or partial forms of persistent common atrioventricular canal (Kiely, Adams, Anderson and Lester[10] and Paul[12]).

The cardiac murmurs in these patients were studied by recording them on magnetic tape and examining the recordings with the cathode-ray oscilloscope and the sound spectrograph. Oscillographs of recordings obtained at the mitral area of the patients shown in Fig. 3, showed a wave form of the complex type which has been found in murmurs of mitral insufficiency in rheumatic heart disease (Harris and Needleman[8]), although there was less evidence of high-frequency components than had been found in the murmurs due to mitral or aortic insufficiency. Spectrographic tracings of these 4 murmurs are shown in Fig. 4. Here again the tracings show evidence of complex mixtures of vibrational components, by the diffuse blackening in the area corresponding to the murmur, as was found elsewhere in the case of murmurs of mitral insufficiency (Harris, Saltzman, Needleman and Lisker[9]), but, again, the upper limit of frequency is generally lower in these

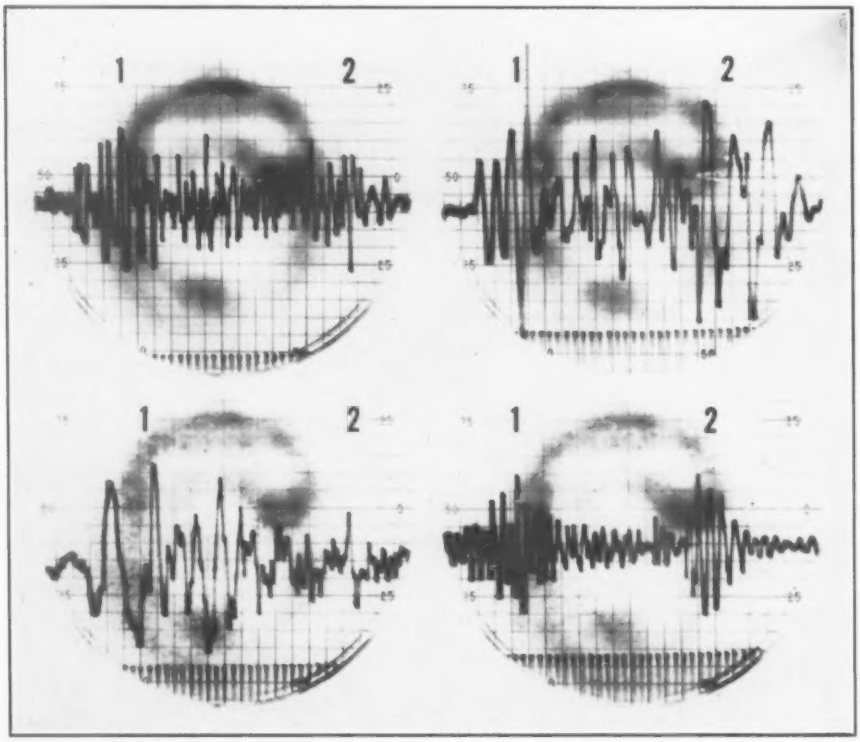


Fig. 3.—Oscillographs of the cardiac sounds recorded at the apex of each of the children with congenital valvular insufficiency. Marker below each oscillograph indicated time in units of 0.01 second. The numbers 1 and 2 indicate the oscillations due to the first and second heart sounds, respectively.

tracings than those found in the case of the rheumatic valvular insufficiencies.

Because of the similarity of the clinical findings among these 4 patients, the details of only one case will be presented.

Case Report. CASE 3.—(R.M.): This 7-year-old white boy visited the Rheumatic Fever Clinic of the Philadelphia General Hospital for the first time in August, 1955, having been referred for evaluation of a cardiac murmur discovered in the course of a routine physical examination at school.

The patient led a normal, active life. At no

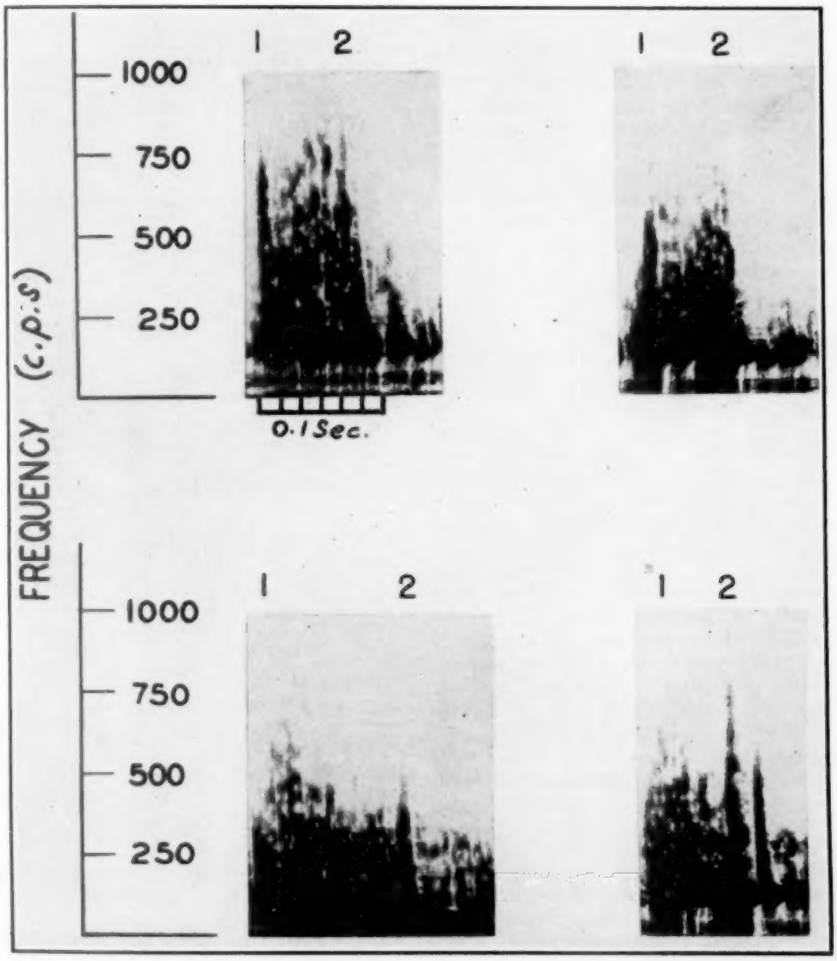


Fig. 4.—Cardiac sound spectrograms taken of these 4 patients. In these graphic representations, the horizontal axis is that of time, the vertical axis is that of frequency of vibration, and the degree of darkening of the paper at any point represents the relative intensity of the component at the time and frequency corresponding to the co-ordinates of that point. In each spectrogram the numbers 1 and 2 are marked above the representation of the first and second heart sounds, respectively.

time did he have any symptoms referable to the cardiovascular system. He was the youngest of 6 children, all of whom were living and healthy. The past medical history was entirely negative. There was no family history of rheumatic fever.

The initial physical examination revealed a well nourished, intelligent 7-year-old white boy with no respiratory distress or cyanosis. The body weight was 49 pounds; body length, 46¼ inches. The only abnormalities noted were those pertaining to the cardiovascular system. All peripheral pulses were present and equal; the blood pressure in the arms was 100/50. The apex beat was in the fifth intercostal space in the mid-clavicular line. The second heart sound at the base was widely reduplicated; a loud third heart sound was heard slightly to the right of the apex. A high pitched, holosystolic, blowing murmur was present at the apex and was transmitted to the left posterior axillary line and to the back on both sides. To the right of the apex a short low pitched mid-diastolic murmur was audible; a short, low pitched systolic murmur was also present at the base. No thrills were palpable. The liver and spleen were not enlarged.

Laboratory studies revealed a hemoglobin level of 12.7 gm. %; a corrected erythrocyte sedimentation rate of 7 mm. per hour; antistreptolysin titer, 96; antihyaluronidase titer, 128. An electrocardiogram demonstrated a PR interval of 0.18 second at a cardiac rate of 113 per min., left axis deviation in the limb leads, and evidence of biventricular hypertrophy in the precordial leads. Roentgenograms of the chest (Fig. 1) revealed a slight degree of cardiomegaly; the pulmonary artery segment was prominent and the peripheral pulmonary vascular markings were slightly exaggerated. There was definite evidence of right atrial enlargement and a small aortic arch.

After a 2-year period of observation in the Rheumatic Fever Clinic, during which penicillin prophylaxis was administered, the patient was admitted to the pediatric wards of the Philadelphia General Hospital for further evaluation of the etiology of his heart disease. A right heart catheterization was performed which yielded evidence of a significant left to right shunt at the atrial level, thus demonstrating the presence of a congenital cardiac anomaly (Table 3). In addition to the interatrial communication, some deformity of the atrioventricular valve leaflets could be presumed because of the electrocardiographic findings. The patient has been observed for two years subsequent to the cardiac catheterization, during which interval penicillin prophylaxis has not been maintained, and has remained entirely well.

In addition to the 4 patients described above, a fifth patient with ostium primum syndrome and a systolic blowing murmur at the apex has since been encountered, in whose case the diagnosis of rheumatic heart disease had not been entertained. This patient was studied by cardiac catheterization and also by the intracardiac sound-mapping technique (Wallace *et al.*[16]). In this 6-year-old child an arteriovenous shunt was demonstrated at the atrial level only; no pulmonary hypertension or arterial unsaturation was found. A loud and harsh systolic murmur was recorded with the catheter tip in the right ventricle indicating that a second arteriovenous shunt was probably present at the ventricular level. With the intracardiac sound catheter a soft systolic murmur was also recorded in the right atrium. In view of the large interatrial communication, it is not unreasonable to assume that this murmur had its origin in the left heart and resulted from regurgitation of blood from the left ventricle into the left atrium because of deformity of a mitral valve leaflet. In addition, a soft systolic murmur was found in recordings from the main pulmonary artery, a common finding in patients with increased pulmonary blood flow. A mid-diastolic murmur noted in the region of the apex by external auscultation was not recorded from the right side of the heart by the intracardiac catheter. This may be attributed to the fact that the primary site of origin of this diastolic murmur was in the left ventricle.

Discussion. DIFFERENTIATION OF VALVULAR INSUFFICIENCY OF RHEUMATIC AND CONGENITAL ORIGIN. The considerably different methods of management of patients with mitral insufficiency re-

sulting from rheumatic fever as compared to valvular insufficiency associated with a congenital malformation of the atrioventricular valve leaflets makes the differentiation of these two lesions of clinical importance. In the rheumatic child, a conservative course with periodic observation and a program of antibiotic prophylaxis against streptococcal infection is followed after it has been established that the rheumatic fever is inactive. In the patient with a congenital cardiac anomaly that includes regurgitation at the atrioventricular valve, the need for surgical repair of the valve and associated defects with the use of a heart-lung apparatus must ultimately be considered. That regurgitation of blood from the left ventricle into the left atrium does occur in the presence of this congenital deformity of the atrioventricular valve leaflets has been confirmed at the time of surgery by digital palpation of the regurgitant jet entering the left atrium during ventricular systole (Blount, Balchum and Gensini[1]).

There are certain clinical features which may be of limited usefulness in determining the etiologic variety of valvular insufficiency in a given situation. A positive family history of rheumatic fever favors that etiology. On the other hand, discovery of the cardiac murmur in infancy suggests a congenital cardiac defect. The higher absolute incidence of rheumatic fever is likely to influence the observer toward the rheumatic etiology and away from the rare congenital cardiac anomaly.

Auscultation of the apical murmur itself provides no aid in differentiating these two varieties of valvular insufficiency. Wide reduplication of the second heart sound in the pulmonic listening area was consistently present in our patients with the arteriovenous shunts, but some reduplication of the second heart sound may be observed in many normal children. A left parasternal low-pitched systolic murmur was a consistent finding in the patients with the congenital lesion, but this may or may not be present in subjects with rheumatic mitral insufficiency, as well as in normal children.

On the other hand, study of the electrocardiograms and roentgenograms obtained from these children provided reliable information for making the etiologic differentiation of the valvular insufficiency. The paradoxical combination of a marked left axis deviation in the limb leads of the electrocardiogram and evidence of either right ventricular hypertrophy or combined ventricular hypertrophy in the precordial leads is consistently found in patients with complete or partial forms of persistent common atrioventricular canal (Friedman and Ash[3], and Toscano-Barbosa, Brandenburg and Burchell[14]). Endocardial cushion defects (Campbell and Missen[2], and Paul[12]) or the ostium primum syndrome (Kiely, Adams, Anderson and Lester[10]) are other names which have been applied to this group of congenital cardiac anomalies. The patient recently reported as having an isolated ostium primum defect and no atrioventricular valve deformity (Blount, Balchum and Gensini[1]), showed a right axis deviation and right ventricular hypertrophy, the picture that is seen in the usual varieties (ostium secundum) of isolated atrial septal defects. It is likely, then, that the peculiar electrocardiographic configuration in patients with defects of the ostium primum type is related in some way to the associated deformity of the atrioventricular valve leaflets. Some patients with isolated rheumatic mitral insufficiency may also demonstrate left axis deviation, but show evidence in the precordial leads of either left ventricular hypertrophy or no ventricular hypertrophy. Finally, a

prolongation of the PR interval is common in rheumatic heart involvement as well as in the congenital anomaly under discussion.

In the routine roentgenograms of the chest, cardiac enlargement may be common to both lesions. The presence of increased peripheral pulmonary vascular markings and a prominent pulmonary artery segment in contrast to a small aortic shadow suggests the presence of an arteriovenous shunt. Left atrial enlargement, present in 18% of children with mitral insufficiency due to rheumatic heart disease (Miller and Wedum[11]) was not evident in any of our patients with insufficiency associated with congenital valve deformity. The contour of the cardiac silhouette with congenital valvular insufficiency is suggestive of right ventricular hypertrophy with a raised blunted apex and projection of the left heart border toward the left lateral chest wall. In some patients evidence of left atrial and left ventricular enlargement has been noted in addition to the right heart enlargement. With isolated rheumatic mitral insufficiency, roentgenographic evidence of left ventricular hypertrophy alone is present, with projection of the cardiac shadow to the left and downward in the anterior-posterior view.

The definitive method of differentiating the two varieties of valvular insufficiency under consideration is by right heart catheterization. The demonstration of an arteriovenous shunt entering the right atrium or the right ventricle, or both, indicates the presence of a congenital malformation. In the recent reviews dealing with endocardial cushion defects (Kiely *et al.*[10] and Paul[12]), the point is made that failure to find a second rise in oxygen content at the ventricular level is not unusual even in cases proved at necropsy or operation to have a ventricular septal defect. This phenomenon may be explained by the very high percentage increase in oxygen content required to produce a significant change at the ventricular level after a large arteriovenous shunt entering the atrium has raised the oxygen content of the blood in that chamber to a point which is close to systemic arterial oxygen levels.

Finally, the combination of a congenital defect of the atrial or ventricular septum plus an acquired rheumatic mitral insufficiency could produce cardiac catheterization findings similar to those observed in the ostium primum syndrome. In this situation the information obtained from the roentgenograms and electrocardiogram may permit differentiation of this combination of lesions.

SIMILARITY OF CARDIAC MURMURS IN CONGENITAL AND RHEUMATIC HEART DISEASE. A variety of congenital cardiac anomalies produce cardiac murmurs similar to those heard in children with rheumatic heart disease. For instance, the murmur of rheumatic aortic insufficiency is simulated by the early diastolic decrescendo insufficiency-type murmur associated with a congenital bicuspid semilunar valve; pulmonary hypertension may be associated with insufficiency of the pulmonary valve in patients with congenital heart disease. Dilatation of the mitral valve ring occurring in those congenital cardiac anomalies which produce overwork of the left heart (for example, coarctation of the aorta, patent ductus arteriosus), may be associated with an apical systolic blow similar in quality to that of rheumatic mitral insufficiency. In addition, lesions involving the left heart are frequently associated with short early-diastolic murmurs at the apex, which are similar to those observed during active rheumatic carditis. Finally, congenital mitral stenosis can

produce a mid-diastolic or presystolic rumbling murmur which cannot be differentiated from a murmur caused by the same lesion of rheumatic origin.

In other acquired conditions murmurs may be encountered which mimic those found in rheumatic heart disease. Systolic and presystolic apical murmurs indistinguishable from those of rheumatic origin have been observed in a child with Hurler's Disease (Vanace, Friedman and Wagner[15]) who was found at postmortem examination to have a marked deformity of the mitral valve. Deformity of the mitral and aortic valves with endocardial fibroelastosis may also produce murmurs of similar acoustic characteristics. In the syndrome of "idiopathic hypercalcemia of infancy with failure to thrive" a murmur suggestive of aortic stenosis has been heard (Rashkind, Golinko and Arcasoy[13]). Finally, hyperthyroidism in childhood may be accompanied by the presence of an apical blowing murmur of similar quality.

PHYSICAL STUDIES OF ACOUSTIC QUALITIES OF THE APICAL MURMURS DUE TO THE PARTIAL FORM OF PERSISTENT COMMON ATRIOVENTRICULAR CANAL. In earlier studies from this laboratory, oscillographic examinations were carried out by phonocardiography (Harris[5], Harris and Friedman[6] and Harris, Friedman and Haub[7]) and cathode-ray oscillography (Harris and Needleman[8]) of the two major innocent cardiac murmurs, the precordial "twanging-string" murmur of Still and the pulmonic-systolic murmur, and of some organic cardiac murmurs, those of mitral and aortic insufficiency of rheumatic heart disease, and those accompanying some lesions of congenital heart disease which produce systolic murmurs audible in the left upper parasternal area. Tape recordings of the murmurs were also studied by sound spectrography (Harris, Saltzman, Needleman and Lisker[9]). In general the oscillographic records of the organic murmurs examined showed higher complexity of wave forms than the samples of the innocent murmurs, and, correspondingly, in the spectrographic analyses, the organic murmurs showed a wider scattering of frequencies of vibrations than did the innocent murmurs tested, as shown by diffuse blackening of the area of the tracing corresponding to the murmur. The oscillographic traces of murmurs due to persistent common atrioventricular canal, shown in Fig. 3, show a complexity of wave-form comparable to those found in murmurs of mitral and aortic insufficiency, with evidence of less vibrational energy at the higher frequencies than in the tape recordings of the murmurs due to rheumatic valvular insufficiencies. The spectrographic traces of these murmurs are also similar in type to those obtained previously with rheumatic mitral and aortic insufficiency, again with evidence of somewhat less vibrational energy recorded at the higher frequency levels. The similarity between the apical blowing murmurs of persistent common atrioventricular canal and those of rheumatic mitral insufficiency, by these two kinds of analysis, is not surprising, since they probably have the same mechanical basis, that is, turbulent back-flow of blood through the atrioventricular valve ring during ventricular systole. The difference between the graphic representations of these two kinds of murmurs, that is, the indication of relatively less vibrational energy in the higher frequency range in the recordings of murmurs due to persistent common atrioventricular canal may well be due to the presence in these children of the low-frequency parasternal systolic murmur mentioned above. Since there is an upper limit to the total intensity of vibrations which

are recorded with a given apparatus, the addition by the parasternal murmur of vibrational energy in the low-frequency range would cause a decrease in the relative intensity of higher frequency vibrational elements in the recordings of the apical murmurs in children with the congenital variety of valvular insufficiency.

Summary. 1. Four children have been encountered among a large group of rheumatic subjects with high pitched systolic blowing murmurs at the apex in whom physiologic studies proved that the murmurs resulted from a congenital deformity of the atrioventricular valve leaflets rather than from the more common rheumatic heart disease.

2. The clinical features which permit a differentiation of mitral insufficiency of rheumatic origin from the complex congenital anomaly associated with atrioventricular valve deformity are reviewed.

3. Oscillographic and spectrographic traces of the cardiac murmurs of these patients are presented, and the similarities and differences of these from traces obtained in rheumatic mitral insufficiency are discussed.

REFERENCES

1. **Blount, S. G., Balchum, O. J.,** and **Gensini, G.:** Circulation, **13**, 499, 1956.
2. **Campbell, M.,** and **Missen, G. A. K.:** Brit. Heart J., **19**, 403, 1957.
3. **Friedman, S.,** and **Ash, R.:** A.M.A. Am. J. Dis. Child., **93**, 619, 1957.
4. **Friedman, S.,** and **Wells, C. R. E.:** J. Pediat., **49**, 410, 1956.
5. **Harris, T. N.:** Am. Heart J., **50**, 805, 1955.
6. **Harris, T. N.,** and **Friedman, S.:** Ibid., **43**, 707, 1952.
7. **Harris, T. N., Friedman, S.,** and **Haub, C. F.:** Pediatrics, **3**, 845, 1949.
8. **Harris, T. N.,** and **Needleman, H. L.:** Am. Heart J., **52**, 887, 1956.
9. **Harris, T. N., Saltzman, H. A., Needleman, H. L.,** and **Lisker, L.:** Pediatrics, **20**, 7, 1957.
10. **Kiely, B., Adams, P., Anderson, R. C.,** and **Lester, R. G.:** A.M.A. Am. J. Dis. Child., **96**, 381, 1958.
11. **Miller, J. H.,** and **Wedum, B. G.:** Ibid., **78**, 703, 1949.
12. **Paul, M. H.:** Pediat. Clin. N. America, **5**, 1011, 1958.
13. **Rashkind, W. J., Golinko, R.,** and **Arcasoy, M.:** In preparation.
14. **Toscano-Barbosa, E., Brandenburg, R. O.,** and **Burchell, H. B.:** Proc. Staff Meet., Mayo Clinic, **31**, 513, 1956.
15. **Vanace, P., Friedman, S.,** and **Wagner, B.:** In preparation.
16. **Wallace, J. D., Brown, J. R., Jr., Lewis, D. H.,** and **Deitz, G. W.:** J. Acoustical Soc. America, **29**, 9, 1957.

SUMMARIO IN INTERLINGUA

Congenite Deformitate del Segmentos del Valvula Atrioventricular, Simulante Insufficientia Rheumatic del Valvula Mitral

1. In un grande gruppo de rheumatic patientes pediatric con sufflante murmures systolic de qualitate acute al apice, quatro subjectos esseva trovate in qui studios physiologic provava que le murmures resultava ab un deformitate congenite del segmentos del valvula atrioventricular e non ab le causa plus commun de tal murmures, *i.e.* ab rheumatic morbo cardiac.

2. Es presentate un revista del aspectos clinic que permitte le differentiation inter insufficientia mitral de origine rheumatic e le complexe anormalitate congenite que es associate con deformitate del valvula atrioventricular.

3. Le manifestationes oscillographic e spectrographic del murmures cardiac in iste patientes es presentate, e le similitudes e le differentias es discutite que existe inter illos e le manifestationes correspondente trovate in le caso de patientes con rheumatic insufficientia mitral.

AORTAL CHOLESTEROL CONCENTRATIONS AFTER LINODOXINE ADMINISTRATION IN DOGS*

By Lawrence J. Milch, Ph.D.†

Lesly G. Robinson, B.S.

Sherman S. Wilson, M.S.

and

Fredrick H. Wilson, Jr., B.S.

(From the Department of Pharmacology and Biochemistry, School of Aviation Medicine, Brooks Air Force Base, Texas)

During the past 3 years a number of drug preparations containing linoleic acid have been marketed by the pharmaceutical industry. Ethical advertistising of these substances has referred to extensive data demonstrating the hypocholesterolemic effect of essential unsaturated fatty acids in man (Ahrens *et al.*[1]), and to the statistical inference that lowered blood cholesterol levels will contribute to reduced arterial "atherogenesis" (Bronte-Stewart, Keys and Brock[2]). Hegsted *et al.*[3] reported that corn oil (55.7% linoleic acid) administration resulted in lowered serum cholesterol concentrations and less vascular sudanophilia in the cholesterol-cholic acid-fed rat, but failed to demonstrate any effect of the unsaturated essential fatty acid administration on cholesterol deposition at the arterial wall. Since arterial cholesterol deposition may be more closely related to the pathogenesis of atherosclerosis than are serum cholesterol levels, it was decided to determine any effect of Linodoxine‡ on the cholesterol concentrations of the aortae and coronary arteries of dogs fed a hypercholesterolemic regimen of excess fat, cholesterol, and propylthiouracil.

Material and Methods. Two groups (L and P) of 6 dogs each were fed identical diets of Ken-L-Ration, lard, cholesterol, and propylthiouracil over a 9- to 11-week period. The diet of the group L dogs was supplemented by the daily addition of 200 ml. of Linodoxine while the group P animals received an equal volume of a placebo mixture prepared by Chas. Pfizer and Co. to be similar in taste, appearance, and consistency to Linodoxine. The placebo mixture differed significantly from the Linodoxine in that (1) coconut oil§ was substituted for safflower oil, and (2) neither pyridoxine nor mixed tocopherols were incorporated. A third group (C) of 6 dogs was maintained over the experimental period on Ken-L-Ration, lard, and propylthiouracil. All animals were presented with equal quantities of the appropriate ration twice daily. No effort was made to control food intake and water was allowed *ad libitum*. The food mixtures were well tolerated and individual weighings of the animals at weekly intervals failed to demonstrate significant change. The diet mixtures, including supplements, were repeatedly analyzed for cholesterol and fat during the experimental

*The contents of this article reflect the personal views of the authors and are not to be construed as a statement of official Air Force Policy.

†Formerly Chief, Department of Pharmacology and Biochemistry, School of Aviation Medicine, USAF. Present address: 6102nd Air Base Wing, APO 328, San Francisco, California.

‡Chas. Pfizer and Co. Safflower oil—78% linoleic acid, 10% oleic acid, and 12% saturated fatty acids.

§2% linoleic acid, 7.3% oleic acid, and 90.7% saturated fatty acids.

period. Cholesterol assays yielded values as follows: diets L and P, 220 mg. per 100 ml.; diet C, 80 mg. per 100 ml. Fat* assays: L, 17.5%; P, 20.5%; C, 10.8%. Gross signs of myxedema could not be observed in any of the animals, suggesting a minimal antithyroid effect of propylthiouracil.

Control blood samples were secured from each dog prior to beginning the dietary regimens and the sampling was repeated at 14-day intervals. Serum assays for cholesterol, lipid phosphorus, and the ultracentrifugal lipoproteins were accomplished on each blood sample (Schlessinger *et al.*[5]). When the average peak concentrations (6th week) of total serum cholesterol were passed, as indicated by measurements at the 8th week, serial sacrifice of the dogs was initiated. One animal from each group was sacrificed by rapid arterial exsanguination on Monday, Wednesday, and Friday of the 10th and 11th weeks. Aortae and coronary arteries were excised, freed of adhering fat and connective tissue, and analyzed for cholesterol concentration (Milch *et al.*[4]). A portion of each artery was reserved for histologic examination.

Results and Discussion. Histologic examination of aortae and coronary arteries revealed several instances of intimal hyperplasia and occasional fragmentation of the internal elastic membrane consistent with atherosclerosis, but the pathosis was randomly distributed throughout the animal groups. Apparently such minimal changes as were observed existed in these dogs prior to the experiment and were thus unrelated to the dietary regimens. Chemical analyses of the coronary arteries yielded the identical average cholesterol values of 1.56 mg. per gm. wet weight for each of the 3 dog groups, a figure also obtained as the average for 26 control dogs sacrificed at 2-week intervals over a year's period and reported previously (Milch *et al.*[4]). Such suggests that the varying dietary regimens failed to influence the cholesterol concentrations of the coronary arteries.

A somewhat different result was obtained when the dog aortae were subjected to chemical analysis for cholesterol. On each sacrifice date (Fig. 1) the cholesterol concentration of the aorta taken from the dog after Linodoxine administration (group L) was lower ($P = <.05$) than the aortal concentration observed in the corresponding animal maintained on the placebo supplement. Excepting the single value for the control (group C) dog obtained on 19 November, aortal cholesterol concentrations recorded for all animals are consistent with the hypothesis that a Linodoxine supplement to a diet containing excess fat and cholesterol will inhibit any associated increased aortal deposition of cholesterol.

This experiment fails to identify the component that confers such suggestive activity on the Linodoxine mixture. It must be noted, however, that although pyridoxine and mixed tocopherols were absent from the prepared placebo, these vitamins are present in abundance in Ken-L-Ration. The remaining difference between the Linodoxine and the placebo is the character of the fatty acids contained in each. Any definitive conclusion on such sparse data becomes hazardous indeed, but these findings suggest that a suitable mixture of dietary fatty acids may, in fact, be antiatherogenic.

Serum total cholesterol and lipid phosphorus concentrations, obtained as a result of serial blood sampling of each dog, were virtually indistinguishable between dog groups fed Linodoxine and placebo supplements. Neither the cholesterol:lipid phosphorus ratio nor that fraction of total cholesterol transported as β-lipoprotein† was consistently altered in the Linodoxine-fed dogs. Further fractionation of the

*Gravimetric determinations for fat involving extraction with petroleum ether and evaporation to dryness is expected to give falsely low values for the more labile unsaturated oils; thus accounting for the analytical difference between diets L and P.

†All lipoproteins with densities ≤ 1.063 are isolated in the preparative ultracentrifuge and analyzed for cholesterol.

β-lipoproteins in the analytical ultracentrifuge, however, was somewhat more fruitful. Pronounced trends toward increased levels of the S_f^o 0–12 classes and simultaneous decreases of the S_f^o 12–400 classes of serum lipoproteins were associated with Linodoxine administration. When these values were combined into a ratio $\frac{S_f^o\ 12–400}{S_f^o\ 0–12}$, significant discrimination between Linodoxine dogs and placebo dogs could be recorded. These data (Table 1) indicate a uniform plus

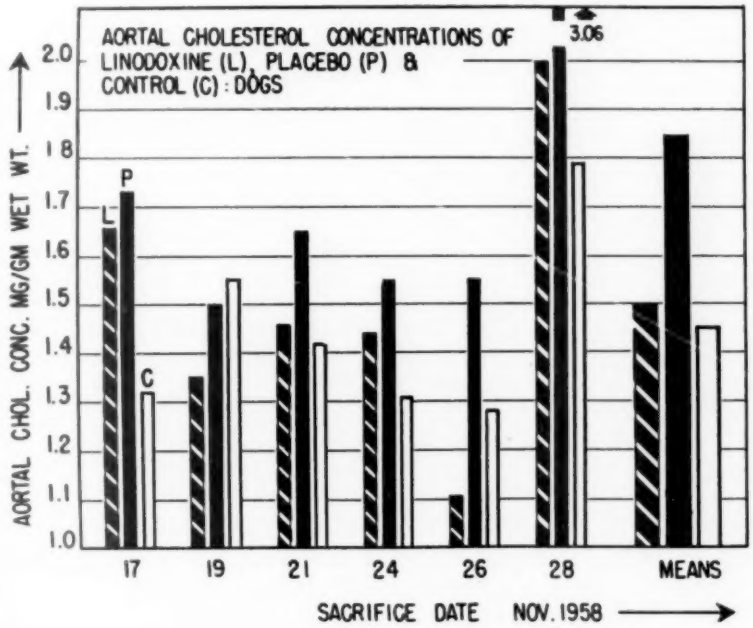


Fig. 1

TABLE 1.—RATIOS OF LIPOPROTEIN CONCENTRATIONS $\frac{S_f^o\ 12–400}{S_f^o\ 0–12}$; PRE-DIET AVERAGE MAINTENANCE VALUES DURING THE DIETARY PERIOD (MV), AND NET CHANGES (Δ) FOR LINODOXINE, PLACEBO AND CONTROL DOGS

Linodoxine Supplement			*Placebo Supplement*			*Controls*		
PV	*MV*	Δ	*PV*	*MV*	Δ	*PV*	*MV*	Δ
304	221	— 083	082	649	567	393	241	— 152
026	348	322	214	222	008	000	402	402
338	087	— 251	099	355	256	039	319	280
383	107	— 276	041	512	471	052	070	018
153	288	135	138	320	182	280	356	076
104	311	207	047	563	516	094	126	032
Av. 218	227	009*	103	438	333†	143	252	109*

*Not significant
†Highly significant, P = <.01

change in the ratio $\frac{S_{12-400}}{S^{o}_{f\ 0-12}}$ between the control sample and the mean of all observations taken during the period of experimental feeding among the dogs in the placebo group. Linodoxine was apparently associated with a reversal of this trend, inasmuch as control-dietary changes in the ratio for the Linodoxine-fed dogs are statistically indistinguishable from those recorded for the group C animals.

Summary. Linodoxine was added to the diet of 6 dogs fed excess fat, cholesterol and propylthiouracil over a 9- to 11-week period. Administration of this drug mixture was associated with significantly decreased concentrations of aortal cholesterol as compared to a simultaneously maintained group of dogs fed the same diet containing a placebo mixture of coconut oil in place of Linodoxine. Linodoxine was also associated with a significant shift of serum β-lipoproteins towards classes of higher density, a reversal of the trend noted in the placebo-fed dog group.

ACKNOWLEDGMENT: Pathologic examination of arterial tissue described in this study was accomplished by Captain Robert A. Brooks, Department of Pathology, School of Aviation Medicine, USAF.

REFERENCES

1. **Ahrens, E. H., Jr., Insull, W., Jr., Blomstrand, R., Hirsch, J., Tsaltas, T. T.,** and **Peterson, M. L.:** Lancet, **1**, 943, 1957.
2. **Bronte-Stewart, B., Keys, A.,** and **Brock, J. F.:** Lancet, **2**, 1103, 1955.
3. **Hegsted, D. M., Andrus, S. G., Gotsis, A.,** and **Portman, O. W.:** J. Nutrition, **63**, 273, 1957.
4. **Milch, L. J. Renzi, A. A., Weiner, N., Robinson, L. G.,** and **Wilson, S. S.:** Proc. Soc. Exper. Biol. & Med., **97**, 56, 1958.
5. **Schlessinger, B. S., Wilson, F. H., Milch, L. J.,** and the Cardiovascular Research Group: Circulation, **19**, 265, 1959.

SUMMARIO IN INTERLINGUA

Concentrationes Aortal de Cholesterol in Canes post Administrationes de Linodoxina

Linodoxina (Chas. Pfizer & Cp.; oleo de carthamo: 78% acido linoleic, 10% acido oleic, e 12% saturate acidos grasse) esseva addite durante periodos de 9 a 11 septimanas al dieta de canes nutrite con excessos de grassia, cholesterol, e propylthiouracil. Le administration de iste mixtura de drogas esseva associate con significative reductiones del concentration aortal de cholesterol in comparation con un simultaneemente mantenite gruppo de controlo nutrite con le mesme dieta excepte que le Linodoxina esseva reimplaciate per un placebo a oleo de coco. Le administration de Linodoxina esseva etiam associate con un transition significative del lipoproteinas beta del sero verso classes de plus alte densitates, per contrasto con le tendentia notate in le canes nutrite con le placebo.

ATRIAL SEPTAL DEFECT
EXPERIENCES IN THE CLINICAL EVALUATION OF 15 CONSECUTIVE CASES OF THE SECUNDUM VARIETY

By Bernard Zylberberg, M.D.

Irving Kass, M.D.

and

Murray S. Hoffman, M.D.

(From National Jewish Hospital at Denver and the University of Colorado School of Medicine, Denver, Colorado)

After evaluating a series of 15 consecutive patients with atrial septal defect of the secundum variety proven by cardiac catheterization, surgery, or necropsy, it became evident that certain variations could be anticipated from standard reports of this anomaly. These experiences are being presented because it is believed that the documentation of some of these discrepancies will be of interest to the clinician involved in the appraisal of such patients.

Material. The case histories of 15 consecutive patients ranging in age from 2 to 51 admitted to National Jewish Hospital at Denver over the past 2 years were studied. This series was composed of 11 females and four males. The cases were reviewed as to history, physical findings, radiologic, electrocardiographic and physiologic data; and surgical or necropsy data when available.

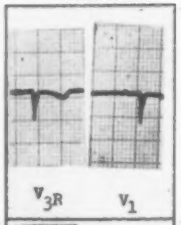
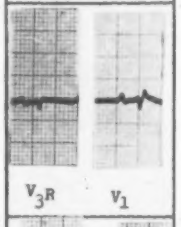
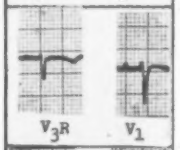
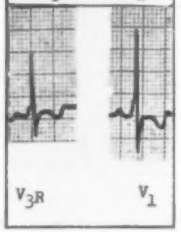
Results. Eleven patients of this group were submitted to surgery and the atrial septal defect of the secundum type was repaired. In one patient, the defect was found at necropsy. (Refer to Table 1.)

Discussion. HISTORY. It has been stated that patients with this type of congenital heart lesion show a distinct failure to gain weight during infancy and childhood, with an increased susceptibility to bronchitis, repeated pneumonic episodes, and even bronchiectasis (Barber, Magidson and Wood[1]). Others, however, have noted in diametrical opposition to this, that the secundum type of defect may cause relatively few symptoms throughout childhood in spite of the presence of an enlarged heart (Bedford, Papp and Parkinson[2], Blount, Munyan and Hoffman[3]). In adult life, one is said to encounter not only frequent bouts of respiratory infections and pneumonia, but also cardiac arrhythmias, congestive cardiac failure, pulmonary hypertension, cyanosis and death (Bedford, Papp and Parkinson[2], Blount, Munyan and Hoffman[3]). In our series of cases, there appeared to be a poor correlation between the size of the defect noted at surgery, the degree of the shunt, and the symptomatology.

Case Reports. CASE 1. S.K., a 10-year-old girl, always thin and underweight, with a history of many respiratory infections, was found to have a relatively small defect which measured only 3 cm. with a small shunt.

CASE 2. C.T., another 10-year-old boy, had a defect measuring 5 cm. and a significant pulmonary:systemic flow ratio (6.4 L. per minute per M^2:2.8 L. per minute per M^2), yet this child exhibited normal growth and development (height 90th percentile; weight 35th percentile) with no history of repeated respiratory infections. In fact, the systolic murmur was first observed at the age of 9,

TABLE I

Name of Patient	*History of Respiratory Illnesses*	*Growth and Development*	*Degree of Incapacity*	*Physical Examination*	*E.K.G.*	*Fluoroscopy*	*Physiological Data*	*Size of Defect*
M.M. 22 Yrs. Female 12599	Nil.	Normal	Increasing dyspnea over past 2–3 yrs.	Ht. 5′ 1½″ Wt. 104 lbs. Syst. murmur at 3rd L.I.S.		Vascularity borderline *(b)* No chamber enlargement	*Pressure*: R.A. 4/1 M.P.A. 17/7 R.V. 26/0 *Flow*: Pulm. Index 6.6 L/M/M² Syst. Index: 3.2 L/M/M² *O_2 Sat.* B.A. 95%	2.5 cm.
H.G. 48 Yrs. Female 12711	Numerous respiratory infections	Poor development	*(a)* Paroxysmal tachycardia *(b)* 'Black-out' spells *(c)* Unable to climb 1 flight of stairs *(d)* Orthopnea	Ht. 5′4″ Wt. 94½ lbs. P_2 acc. with wide redup. Syst. murmur Grade II at 2nd L.I.S.		*(a)* Vascularity increased *(b)* Overall size of heart incr. *(c)* Pulm. artery segment prom. *(d)* R. atrium enlarged	*Pressure*: R.V. 85/0 R.A. 99–1 M.P.A. 88/34 *Flow*: Pulm. Index: 18.3 L/M/M² Syst. Index: 3.8 L/M/M² *O_2 Sat.* B.A. 90.4%	4 cm.
A.H. 32 Yrs. Female 12791	Nil.	Normal	Nil.	Ht. 5′6″ Wt. 126 lbs. P_2 acc. R.V. thrust Grade III syst. murmur at 2nd I.S.		*(a)* Slightly increased vascularity *(b)* Increased pulsation of main pulm. artery	*Flow* Pulm. Index: 8.8 L/M/M² Syst. Index: 3 L/M/M² *O_2 Sat*: B.A. 91.2%	5–6 cm.
P.R. 51 Yrs. Male 12837	Nil.	Normal	31 Yrs. first experienced dyspnea while dancing and climbing stairs	Ht. Not recorded P_2 reduplicated R.V. thrust		*(a)* Increased vascularity *(b)* R. ventricular and R. atrial enlargement	*Pressure*: P.A. 45/24 R.A. 4/0 R.V. 42/12 *Flow*: *Pulm. Index*: 2.4 L/M/M_2 Syst. Index: 2 L/M/M² *O_2 Sat*: B.A. 80.4%	*

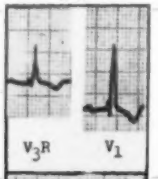
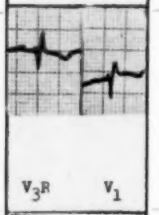
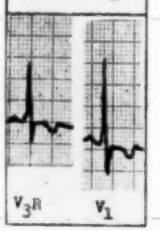
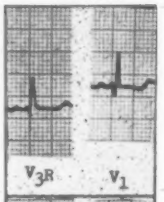
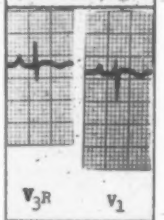
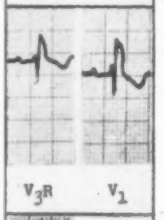
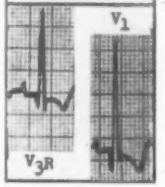
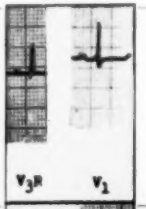
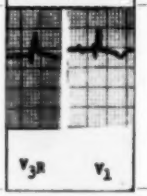
Name of Patient	*History of Respiratory Illnesses*	*Growth and Development*	*Degree of Incapacity*	*Physical Examination*	*E.K.G.*	*Fluoroscopy*	*Physiological Data*	*Size of Defect*
S.K. 10 Yrs. Female 12900	Many Resp. infections	Always been thin and underweight	(*a*) Easily fatigued (*b*) Cyanosis on marked exertion	Ht. 4'6½" Wt. 45 lbs. R.V. thrust Grade III syst. murmur Rt. 2nd I.S.		(*a*) Slightly increased vascularity (*b*) R. atrial and ventricle enlargement	(*a*) *Pressures*: M.P.A. 25/10 R.V. 30/20 (*b*) *Flow*: Pulm. Index: 5.4 L/M/M² Syst. Index: 4.7 L/M/M² B.A. 84.2%	3 cm.
B.B. 31 Yrs. Female 12958	Nil.	Normal	Nil.	Ht. 5'2" Wt. 104 lbs. Grade 3–4 syst. murmur at L. sternal border		(*a*) Increased vascularity (*b*) R. atrial enlargement (*c*) Overall incr. heart size	*Pressure*: R.A. 5/1 R.V. 37/–10 M.P.A. 34/9 *Flow*: Pulm. Index: 2.7 L/M/M² Syst. Index: 1.86 M/M² *O₂ Sat*: 82.9%	1.5 cm.
A.S. 15 Yrs. Male 13055	Pneumonia at 11 mos. and 24 mos. 1952 upper respiratory infections and fainting spell.	Normal	Fainting episodes	Ht. 45" Wt. 92 lbs. R.V. thrust P_2 acc. Grade II syst. murmur at 2nd I.S.		(*a*) Vascularity increased (*b*) Prominent R. ventricle R. atrial enlargement	*Pressure*: M.P.A. 35/8 R.V. 46/–1 R.A. 4/1 *Flow*: Pulm. Index: 24 L/M/M² Syst. Index: 5 L/M/M² *O₂ Sat*: B.A. 92.6%	**
C.T. 10 Yrs. Male 13102	Pulm. T.B. at 9 yrs. of age	Normal	Nil.	Ht. 53¼" Wt. 64¾ lbs. (Ht. 90th percentile) (Wt. 35th percentile) P_2 acc. R.V. thrust Grade 2–3 syst. murmur at 2nd I.S.		(*a*) Increased vascularity (*b*) R. vent. enlargement R. atrial enlargement	*Pressure*: L.P.A. 28/15 R.A. 6/0 *Flow*: Pulm. Index: 6.4 L/M/M² Syst. Index: 2.8 L/M/M² *O₂ Sat*: B.A. 90.3%	5 cm.

TABLE I (*Continued*)

Name of Patient	*History of Respiratory Illnesses*	*Growth and Development*	*Degree of Incapacity*	*Physical Examination*	*E.K.G.*	*Fluoroscopy*	*Physiological Data*	*Size of Defect*
I.Z. 28 Yrs. Female 13248	1955— pneumonia	Normal	Nil.	Ht. 5′ Wt. 100 lbs. R.V. thrust Grade I syst. murmur at 2nd and 3rd L.I.S. Grade I Mid-diast. murmur at L.L. S.B.		(*a*) Increased vascularity (*b*) R. atrial enlargement (*c*) Pulm. artery prominence	Not catheterized Patient pregnant	**
C.D. 2 Yrs. Female 13298	Frequent upper resp. infections	5 lbs. at birth Poor development	Nil.	Ht. 33½″ Wt. 24½ lbs. P_2 slightly acc. Grade 2–3 syst. murmur. Rt. 2nd & 3rd I.S.		(*a*) Increased vascularity (*b*) Slightly increased prominence of main pulm. artery (*c*) No chamber enlargement	(*a*) *Pressures*: M.P.A. 24/8 R.V. 31/–2 R.A. 3/–1 (*b*) *Flow*: Pulm. Index: 9.1 L/M/M² Syst. Index: 5.6 L/M/M² (*c*) O_2 *Sat*: F.A. 86.2%	2 cm.²
D.W. 21 Yrs. Male 13318	Pneumonia at 3 mos.	Normal	Asymptomatic	Ht. 5′10″ Wt. 145 lbs. R.V. thrust Grade II syst. murmur at 2nd L.I.S. Grade I diast. murmur at 4th L.I.S.		(*a*) Increased vascularity (*b*) R. vent. enlargement R. atrial enlargement	*Pressures*: R.P.A. 32/9 R.V. 37/0/7 R.A. 8/7 *Flow*: Pulm. Index: 9.8 L/M/M² Syst. Index: 2.9 L/M/M² O_2 *Sat*: B.A. 93.9%	4 cm.
I.F.M. 29 Yrs. Male 13403	Nil.	Normal	1951 exertional dyspnea 1956 cyanosis developed and clubbing of fingers and toes	Ht. 5′3″ Wt. 88 lbs. P_2 acc. Grade III syst. murmur at L.S.B. Grade 2–3 diast. murmur at 3rd L.I.S.		(*a*) Vascularity increased (*b*) Pulm. arteries prom. (*c*) R. vent. enlargement (*d*) Overall size inc.	O_2 *Sat*: B.A. 74%	Operation Deferred

Name of Patient	*History of Respiratory Illnesses*	*Growth and Development*	*Degree of Incapacity*	*Physical Examination*	*E.K.G.*	*Fluoroscopy*	*Physiological Data*	*Size of Defect*
M.V. 10 Yrs. Female 13412	Nil.	Normal	Since 6 yrs. Mild exertional dyspnea on walking—also mild dyspnea reading	Ht.: 54″ Wt. 88 lbs. Grade II syst. murmur at 2nd I.S.		(*a*) Increased vascularity (*b*) R. vent. enlargement	*Pressure*: M.P.A. 30/12 R.V. 29/12 R.A. 9/5 *Flow*: Pulm. Index: 9 L/M/M² Syst. Index: 5 L/M/M² O_2 *Sat*: F.A. 93.3%	**
F.L. 22 Yrs. Female 13413	1951 Episode of upper resp. infection	Normal	Nil.	Ht. 5′5″ Wt. 98 lbs. R.V. thrust P_2 accentuated Grade II syst. murmur at 2nd and 3rd I.S. Grade 2 diast. murmur at apex		Increased vascularity of lungs (*b*) R. atrial enlargement (*c*) Increased overall size of heart	(*a*) *Pressure*: M.P.A. 35/12 R.V. 44/0 R.A. 12/4 (*b*) *Flow*: Pulm. Index: 8.4 L/M/M² Syst. Index: 1.44 L/M/M² (*c*) O_2 *Sat*: B.A. 95%	6 cm.
A.S.B. 14 Yrs. Female 13536	Numerous upper resp. infections	Normal	Mild exertional dyspnea	Ht. 5′2″ Wt. 95 lbs. P_2 acc. and reduplicated. R.V. thrust Grade II–III Syst. Murmur at 2nd I.S.		(*a*) Vascularity increased (*b*) Pulm. art. prominent (*c*) R. atrial and R. vent. enlargement	*Pressure*: R.A. 4/2 R.V. 40/0 *Flow*: Pulm. Index: 13.9 L/M/M² Syst. Index: 3/8 L/M/M² O_2 *Sat*: B.A. 94.5%	+1.2 cm.

*L.I.S. = Left intercostal space
R.A. = Right atrium
R.V. = Right ventricle
M.P.A. = Main pulmonary artery
B.A. = Brachial Artery
F.A. = Femoral Artery
†No operation performed

O_2 Saturation = 92% (Normal value for altitude of 5800 feet)
R.A. Pressure = 4/–1 mm./Hg.
R.V. Pressure = 15–25 mm./Hg. –10
M.P.A. Pressure = 15–25 mm. Hg./–6

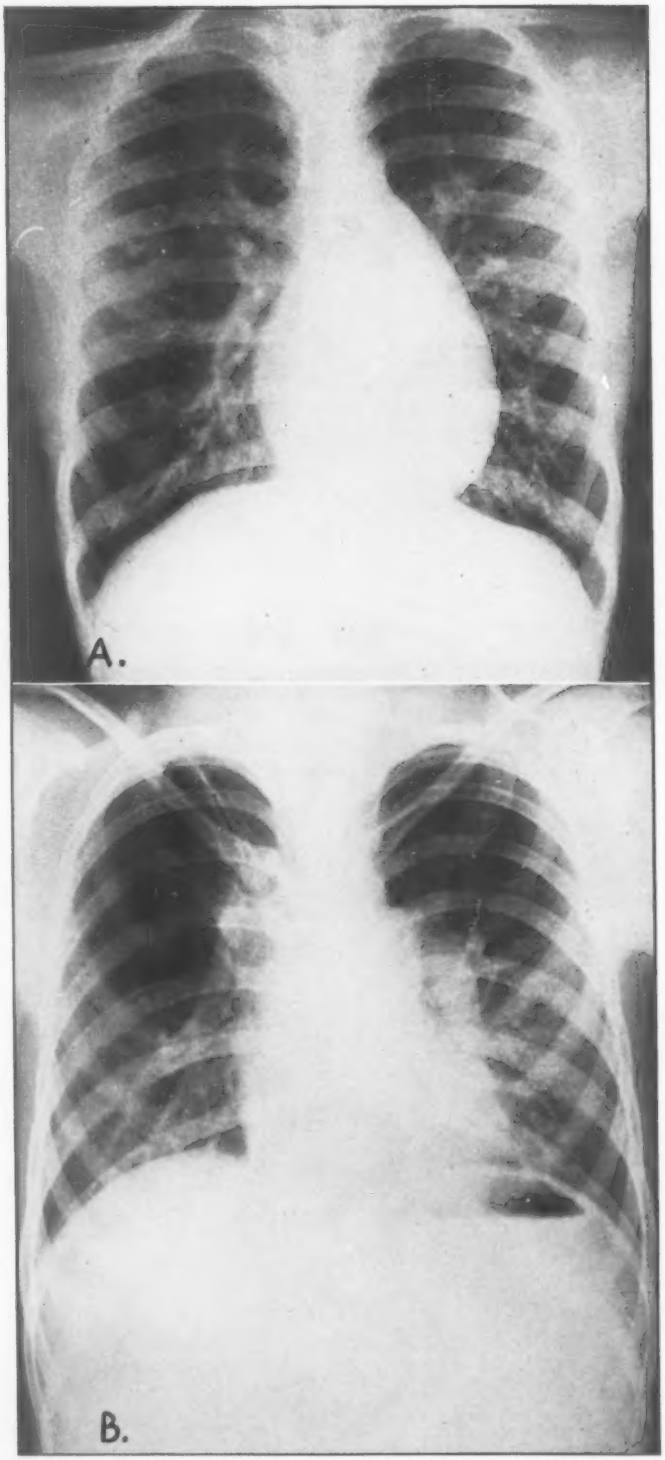


Fig. 1.—PA chest roentgenograms illustrating four types of cardiac silhouette in patients with proven atrial septal defect of the secundum variety. At surgery, all 4 patients were found to have enlarged right atria, hypertrophied right ventricles, and normal left ventricles.

A. Classical configuration with prominent right atrium, right ventricle, main pulmonary artery, and increased lung vascularity.
B. Prominent main, right and left pulmonary arteries, and increased lung vascularity.

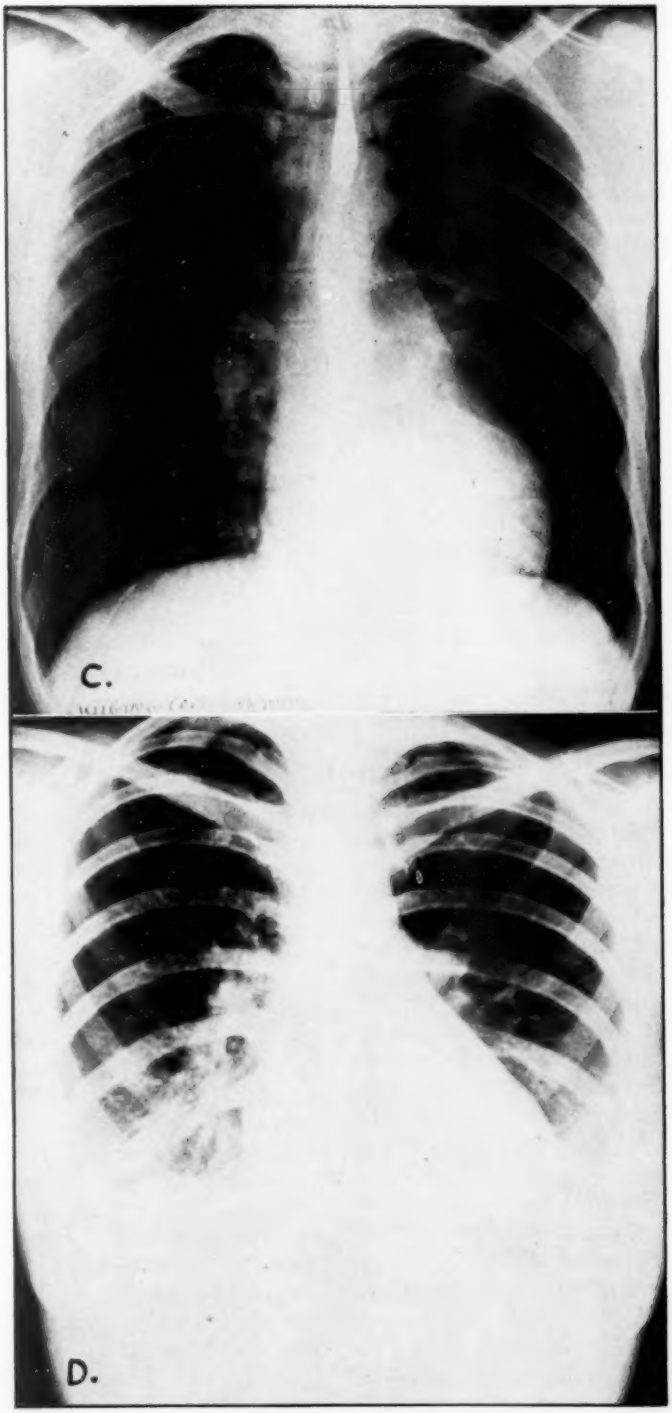


Fig. 1. *(Continued)*

C. Increased lung vascularity and apparently prominent left ventricle.
D. Apparently prominent left ventricle.

when the child was found to have minimal pulmonary tuberculosis.

CASE 3. A.H., a 32-year-old white woman was particularly notable since she displayed normal growth and development and was completely asymptomatic, being a very active mountain climber and skier. An atrial septal defect was first suspected during routine physical examination for employment. Physiological data revealed a pulmonary:systemic flow ratio of approximately 3:1, and at operation, the defect measured between 5 and 6 cm.

PHYSICAL FINDINGS. Patients with atrial defects are said to be underdeveloped, small, and asthenic in build, with narrow chests and tapered extremities (Barber, Magidson and Wood[1]). This has been referred to as the "Gracile Habitus" by Taussig[7], who also commented on the frequency of arachnodactyly and a high-arched palate. Nevertheless, 11 of our patients displayed completely normal growth and development at the time of the examination. The characteristic cardiac findings of the secundum defect, however, (Barber, Magidson and Wood[1], Bedford, Papp and Parkinson[2], Campbell, Neill and Suzman[4], White[8], Wood[9]) were found in the majority of the patients in this series. The accentuated and wide splitting of the second pulmonary sound, fixed on inspiration and expiration, described as an important finding (Campbell, Neill and Suzman[4], White[8]) was definitely present in 10 patients. The character of the pulmonary second sound appeared to be related more to the pulmonary flow rather than to the pulmonary artery pressure.

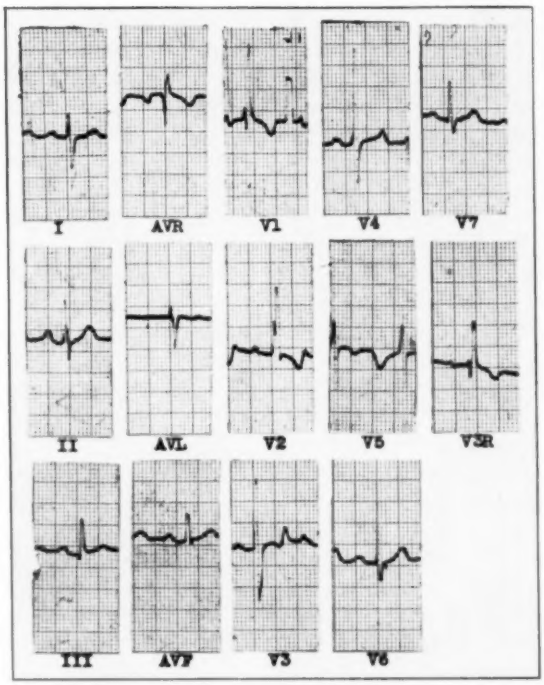
B.B., a 31-year-old woman whose pulmonary second sound was neither split nor accentuated, had a pulmonary artery pressure of 34/9 with a pulmonary index of 2.7 L. per minute per M^2. On the other hand, M.N., a 22-year-old Spanish-American woman, had a pulmonary artery pressure of 17/7 with a pulmonary flow of 6.6 L. per minute per M^2, and in this instance, the pulmonary second sound was accentuated and split.

Patient C.D. had physical findings indistinguishable from a normal heart, but an innocent vibratory left sternal border murmur and a finely split second heart tone on inspiration only. Yet, the pulmonary index was 9.1 L. per minute per M^2, and a 2 cm. defect was found at surgery.

Low frequency mid-diastolic flow murmurs are said to be heard along the left lower sternal border in almost all atrial septal defects of the secundum type where there is a 2:1 pulmonary:systemic flow ratio or more (Bedford, Papp and Parkinson[2], Taussig[7]). In this series of 15 patients there were 3 patients with flow ratios above 2:1 in which no mid-diastolic flow murmurs were audible at the time of examination.

RADIOGRAPHY. It has been reported that the diagnosis of this anomaly is based, in large part, on the roentgenographic findings. These include enlargement of the right heart, especially the right atrium, large main, right and left pulmonary arteries, and increased peripheral lung vascularity. These findings were present in only 5 patients. In some instances, there were right ventricular and right atrial enlargement with increased vascularity, but no prominence of the main pulmonary artery. In others, the right atrium and ventricle were apparently normal in size, yet there was an increased lung vascularity or main pulmonary artery, or both. The variations in the P–A chest films of 4 of the patients in this series are shown in Fig. 1.

ELECTROCARDIOGRAM. Barber, Magidson and Wood[1], in their series of 64 patients, found that right bundle branch block, complete or partial, occurred in 95% of cases and stated that the diagnosis of atrial septal defect



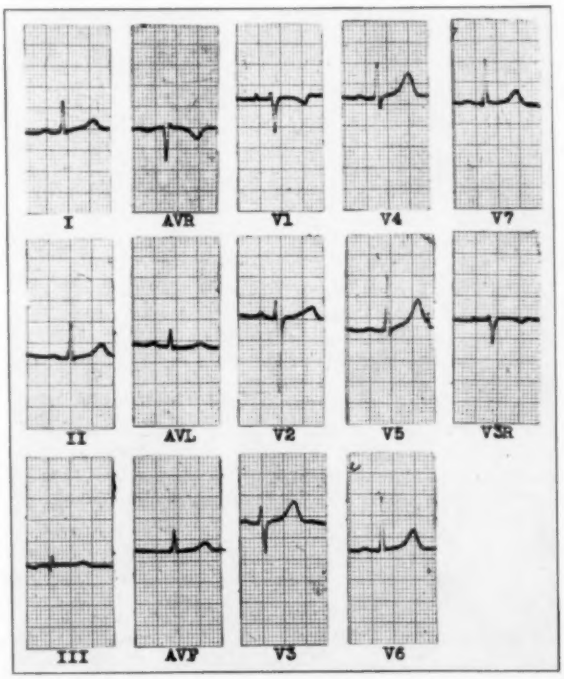


Fig. 2.—Two varieties of electrocardiograms in patients with proven atrial defects of the secundum variety. The tracings ranged from normal, to the classical "incomplete right bundle branch block."

was almost untenable in its absence. In the group of patients here reported, there were 5 patients whose electrocardiogram revealed an rSR′ pattern in the right precordial leads where the QRS measured 0.10 seconds or less. In these same instances it was observed that the secondary R waves were tall. In one additional case there was also a notched R wave. These electrocardiograms were interpreted as being consistent with right ventricular outflow tract hypertrophy.

Prolonged PR intervals were first noted by Bedford, Papp and Parkinson[2]. In 19 of their cases, the PR interval measured 0.20 seconds or more. With the exception of 3 patients, all electrocardiograms revealed a PR interval ranging from 0.12 to 0.18 seconds.

Right axis deviation is said to be found in almost all cases with this anomaly (Barber, Magidson and Wood[1], Bedford, Papp and Parkinson[2], Dexter[5]). These findings occurred in 7 instances in this series, and in 2 cases, the electrocardiogram showed left axis deviation. In the previously cited case, A.H., the electrocardiogram was entirely normal in spite of a 3:1 pulmonic:systemic flow ratio and a large defect.

Summary. Fifteen consecutive cases with atrial septal defect of the secundum variety have been presented. An analysis of clinical findings, radiologic, electrocardiographic, and physiologic data was made and certain discrepancies were noted. These were: 1. There appeared to be poor correlation between the size of the defect, noted at surgery, degree of shunt, and symptomatology. Two instances of 10-year-old children were cited. One, had a history of many respiratory infections, and a defect measuring 3 cm. The other with a larger defect and shunt, and normal growth and development.

2. Three patients with a pulmonary:systemic flow ratio of 2:1 and over, in which no mid-diastolic flow murmurs were audible at the time of examination.

3. Only 5 patients in this series of 15, with the characteristic roentgenographic findings of atrial septic defect.

4. Five patients in whom rSR′ was observed in the right precordial leads. This was interpreted as right ventricular outflow tract hypertrophy. It is concluded that in evaluating patients for this congenital defect, the clinician must be prepared to integrate certain discrepancies.

REFERENCES

1. **Barber, J. M., Magidson, O.,** and **Wood, P.:** Brit. Heart J., **12**, 277, 1950.
2. **Bedford, D. E., Papp, C.,** and **Parkinson, J.:** Ibid., **3**, 37, 1941.
3. **Blount, S. G., Jr., Munyan, E. A., Jr.,** and **Hoffman, M. S.:** Am. J. Med., **22**, 784, 1957.
4. **Campbell, M., Neill, C.,** and **Suzman, S.:** Brit. Med. J., **1**, 1375, 1957.
5. **Dexter, L.:** Brit. Heart J., **18**, 209, 1956.
6. **Nadas, A. S.:** Pediatric Cardiology. Philadelphia: W. B. Saunders Co., p. 285, 1957.
7. **Taussig, H. B.:** Congenital Malformations of the Heart. New York: The Commonwealth Fund, p. 358, 1947.
8. **White, P. D.:** Heart Disease, 4th ed. New York: MacMillan Co., p. 310, 1951.
9. **Wood, R.:** Diseases of the Heart and Circulation. London: Eyre and Spottiswoode, Ltd., Chapt. VII, 1950.

SUMMARIO IN INTERLINGUA

Defecto Atrio-Septal

Experientias in le Evalutation Clinic de 15 Casos Consecutive del Varietate in que le Septo Secunde es Implicate

Es presentate 15 casos consecutive de defecto atrio-septal del varietate in que le septo secunde es implicate. Esseva interprendite un analyse del constatationes

clinic e del datos radiologic, electrocardiographic, e physiologic, e certe discrepantias esseva notate.

1. Pauc correlation pareva exister inter le dimensiones del defecto notate al operation chirurgic, le grado de derivation, e le symptomatologia. Es mentionate le casos de 2 patientes pediatric de 10 annos de etate. Le prime habeva un historia de multe infectiones respiratori, sed su defecto mesurava solmente 3 cm in diametro. Le altere, in qui le defecto e le derivation esseva plus considerabile, se monstrava normal in crescentia e disveloppamento.

2. In 3 patientes con un proportion inter fluxo pulmonar e fluxo systemic de 2:1 o plus, nulle murmures de fluxo medio-diastolic esseva audibile al tempore del examine.

3. Solmente 5 del 15 patientes in iste series exhibiva le characteristic aspectos roentgenographic de defecto atrio-septal.

4. In 5 patientes, rSR′ esseva observate in le derivation dextero-precordial. Isto esseva interpretate como indicio de hypertrophia del vias de effluxo dextero-ventricular.

Es concludite que le clinico qui se trova confrontate con le deber de evalutar patientes con iste defecto congenite debe esser preste a integrar certe discrepantias.

SUMMARIO IN INTERLINGUA

(See page 542 for original article)

Le Effecto de Prednisona e 6-Methyl-Prednisolona Super le Diurese Mercurial in Patientes con Refractori Edema Cardiac

Le autores ha observate le restauration del sensibilitate pro mercurio in patientes con refractori edema cardiac como effecto del tractamento con le steroides prednisona e 6-methyl-prednisolona.

Le alleviamento del refractorietate esseva accompaniate del re-apparition de certe criterios laboratorial le quales es characteristic del satisfacente responsa mercurial e le quales es absente in le stato de refractorietate.

Le resultatos de studios del clearance pare indicar que prednisona e 6-methyl-prednisolona es capace—probabilemente per un mechanismo purmente tubular—a restaurar le sensibilitate pro mercurio in patientes con refractori edema cardiac.

BODY FORM, URINARY ESTROGENS, SERUM CHOLESTEROL AND CORONARY ARTERY DISEASE IN ADULT WHITE MALES*

By David M. Spain, M.D.

and

Daniel J. Nathan, M.D.

(From the Department of Pathology, Beth-El Hospital, Brooklyn, New York)

One of the few established facts concerning the pathogenesis of coronary atherosclerosis is the difference in the degree of coronary atherosclerosis that exists at this time between the sexes in the white population of this part of the world (Piel[7], Spain and Bradess[10]). This is particularly marked between the ages of 35 and 50 when the white male shows a markedly higher morbidity and mortality rate from coronary artery disease than does the white female. This has been attributed in part to differences in certain aspects of estrogen metabolism in the sexes. Postmortem studies on the degree of aortic and coronary atherosclerosis in oophorectemized women (Wuest, Dry and Edwards[13]); studies of the effects of various estrogen preparations on experimentally induced atherosclerosis in animals (Peck *et al.*[8]); and the effects of therapeutically administered estrogens on the serum cholesterol level and beta lipoprotein fractions in humans tend to partially support this concept (Gertler, Hudson and Jost[4]). Bauld, Gioner and Milne observed that men with coronary artery disease who were given 17 beta-estradiol excreted more estriol than did control subjects[1]. It has also been observed in both clinical and postmortem studies that the degree of coronary atherosclerosis appears to be more marked in the mesomorphic male than in the other somatotypes (Gertler, Garn and White[3], Gertler *et al.*[5], Spain, Bradess and Huss[11]). For these reasons, this study was undertaken to determine whether the reported differences in the degree of coronary atherosclerosis among the various male somatotoypes might to some extent be associated with variations in urinary estrogen levels, and whether any such variations exist between "normal" males and those with clinical evidence of coronary artery disease.

Because such factors as age, race, ethnic origins, diet, physical activity, cultural background, cigarette smoking, weight, diabetes mellitus, blood pressure and serum cholesterol levels may be implicated in the pathogenesis of coronary atherosclerosis, it was necessary to so select the individuals for the purposes of this study as to minimize the variability of as many of these factors as possible.

Methods. The individuals in this study were all white males of the same ethnic origin (Jewish), from a fraternal organization whose members have been appearing voluntarily for the past 3 years at this clinic for cancer detection and cardiac survey. It was necessary to examine and interview in detail over 700 men in order to obtain approximately 150 men of the various body types with sufficient comparability in their characteristics for the purpose of this study.

*Supported by Grant-in-Aid, H–2692—National Heart Institute Department of Health, Education and Welfare.

These men were all long-term residents of the same geographic area. Most of them had been born and raised in this area. They had essentially the same cultural and dietary habits. The diet of the group as a whole was high in daily caloric intake and contained a relatively large amount of saturated animal fat. The frequency of obesity in the group was high. The individuals were all employed in sedentary or moderately active occupations and rarely engaged in any physical activity or sports in their leisure time. The information as to their occupation, dietary habits, marital status, and the like was obtained on the basis of a careful personal interview conducted by the same interviewer throughout the entire study, utilizing the same technique for each individual.

A complete physical examination and detailed medical history with special emphasis on the cardiovascular system were obtained. This included very careful questioning concerning any symptoms related to past or present heart disease. Weight history for the previous 5- to 10-year period was obtained. A 12-lead electrocardiographic tracing, a barium swallow with fluoroscopy, and a 70 mm. chest film with 2 meter target distance was obtained on each individual. Proctoscopy and eye ground examination were routinely performed. Complete urinalysis included microscopic study of the sediment. Hematologic examination consisted of hemoglobin determination, hematocrit, white blood cell count and differential. Serum cholesterol determination was performed according to a modification of the Schoenheimer-Sperry method. Initially serum beta lipoprotein pattern was determined according to the ultracentrifuge technique of Gofman but was later discontinued as adding unnecessary expense and detail for the purposes of this study. The blood for serum cholesterol was drawn on the same day of the week (Monday) at the same time (5 P.M.) from these individuals, who had been fasting since noon, when they had been instructed to have a light lunch consisting of toast and tea. All of the serum cholesterol determinations were performed in duplicate.

The 24-hour urinary estrogen output was determined on each individual according to the chemical method devised by Finkelstein[2]. This is a photofluorometric method for the determination of micro amounts of estrogen (estrone-estradiol and estriol) in the urine and is especially designed for achieving a greater degree of accuracy in the urine of males where smaller amounts of estrogenic substances are found. The procedure requires six ether extractions of a 10 ml. aliquot sample of urine and is based on the fact that 85% of phosphoric acid when heated with estrogens will fluoresce. A Farrand fluorometer was used. All determinations were performed in duplicate. The same determinations were also made on a group of pre-menopausal "normal" females for comparison purposes. The individuals continued their usual activity and diet during the period when their urine was collected. Collection of urine was uniformly begun on each individual on a Sunday morning after discarding the first specimen on arising. Collection was continued through the following Monday morning and was delivered to the laboratory where the total 24-hour output was measured and a 50 ml. aliquot sample was frozen until the estrogen determination was made.

The individuals were divided into the various anthropometric types according to the classifications of Sheldon[9]. For the purposes of this study this classification was modified so that the individuals were grouped only according to their dominant somatotypes (mesomorph, endomorph, ectomorph and median). Determination of body form was based upon measurements of height, weight, biachromial and bi-iliac diameters, torso and extremity length, anterior and posterior diameters of chest and estimates of muscularity, configuration, angularity and roundness of body.

Blood pressures were determined generally at the beginning and towards the end of the entire examination. These were taken in a sitting position on the left arm by the same individual in the entire study. For the purposes of this report the lower reading of the two was utilized and any diastolic pressure over 95 mm. was regarded arbitrarily as hypertension.

The cardiac examination and history, as well as the interpretation of the electrocardiograph, was performed by the same individual on all of the cases involved in the study. The electrocardiographic tracings were first interpreted without any knowledge of the clinical stories of the individuals whom they represented. These were then re-read with the complete knowledge of the history and physical examination. Cases were then classified as those with clinical evidence of coronary artery disease if there was a satisfactory history of angina pectoris according to the general criteria for the diagnosis of angina pectoris as utilized in other studies (Conference[12]). A previous history of myocardial in-

farction in the absence of current pathognomonic electrocardiographic changes required positive proof from previous clinical or hospital records. Evidence of myocardial infarction, recent or remote, as indicated by definitive current electrocardiographic changes was acceptable. Questionable cases of angina pectoris or previous myocardial infarctions were excluded from this portion of the study.

As a result of this deliberate selection based upon the examination and screening of 700 men, over 90% of the individuals in this phase of the study were between the ages of 35 and 50. This selection was purposeful in order to limit the number of estrogen determinations because of wide variability in age.

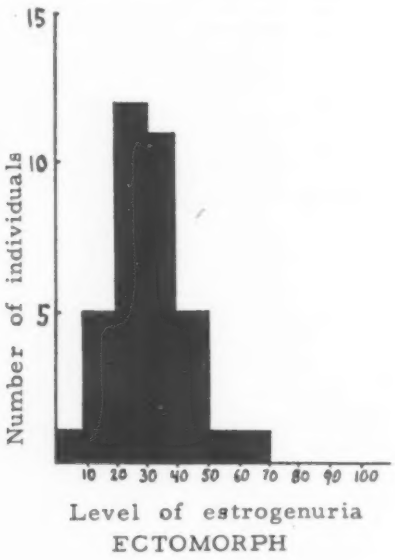


Fig. 1

Results. Examination of the charts (Figs. 1, 2, 3, 4 and 5) reveals that the mean distribution of the estrogenuria levels in the 24-hour specimens was essentially the same in the various somatotypes. There was also no significant difference in the mean distribution of the estrogenuria levels between the entire "normal" groups of various somatotypes and those with clinical evidence of coronary artery disease. The mean estrogenuria level expressed in μg. per 100 ml. of urine was 30 for the ectomorphic group, 33 for the endomorphs, 28 for the mesomorphs, and 25 for the median group. In the group with clinical evidence of coronary artery disease it was 30. In the "normal" females of pre-menopausal age, the lowest 24-hour estrogenuria level obtained was 46 μg. per 100 ml. This was significantly above any of the mean levels in the various male groups studied.

There was no special distribution of estrogenuria levels according to age within the limits of the group studied (See Table 1). There was also no correlation between estrogenuria levels and the serum cholesterol levels in either the "normal" group or those with coronary artery disease (See Tables 2 and 3). However, there was the usual partial correlation of serum cholesterol levels with clinical coronary artery disease to the same extent as observed in other studies. This particular group under study was deter-

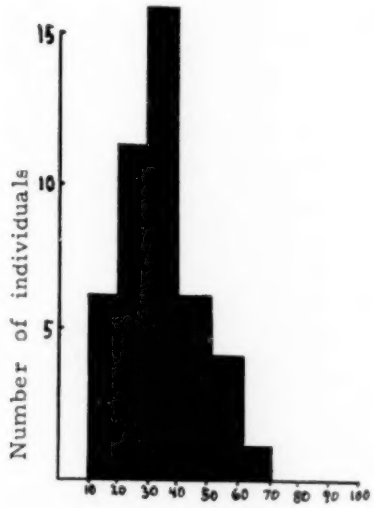

15
10
5
Number of individuals
10 20 30 40 50 60 70 80 90 100
Level of estrogenuria
ENDOMORPH

Fig. 2

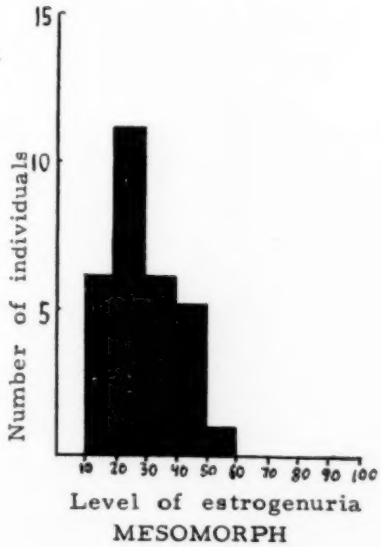

15
10
5
Number of individuals
10 20 30 40 50 60 70 80 90 100
Level of estrogenuria
MESOMORPH

Fig. 3

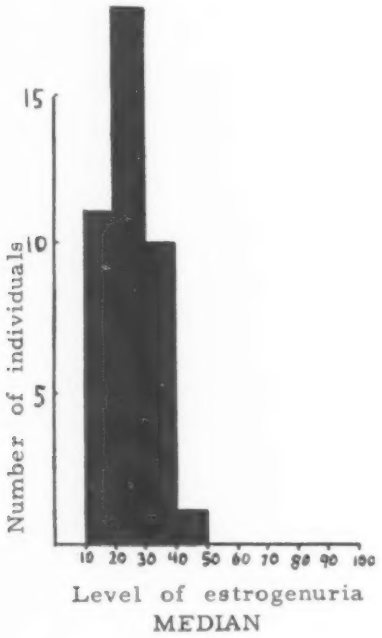


Fig. 4

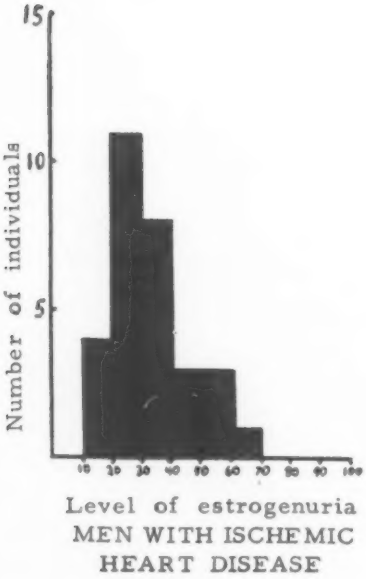


Fig. 5

Figs. 1, 2, 3, 4, 5.—Distribution of levels of 24-hour urinary estrogens (μg./100 ml.) in various somatotypes and in males with clinical coronary artery disease.

mined to be free from any clinical evidence of liver disease, diabetes mellitus, thyroid dysfunction or significant hypertension.

Discussion. In this group of "comparable" and "normal" males there were no differences in the distribution of 24-hour urinary estrogen levels estrogen excretion may not accurately reflect differences in estrogen metabolism, or differences in degrees of femininity. However, to the extent that 24-hour urinary estrogen excretory patterns reflect these things, these do not offer an explanation or a lead into the reasons for the differences in degree of coronary atherosclerosis among various males. Differences in degree of estrogen excretion probably must be of the magnitude of the differences that exist between the two sexes before this can be considered a factor of any significance. This is supported to some extent by the fact that doses of estrogenic substances required to alter among the various somatotypes. There were also no differences between these "normals" and those with clinical evidence of coronary artery disease. It is recognized that currently available biochemical methods for the determination of urinary estrogen levels are not all that are desired. It is also recognized that the pattern of urinary

TABLE 1.—AGE AND URINARY ESTROGEN LEVELS IN "NORMAL" MALES

Urinary Estrogen Levels (μg./100 ml.)

Age	*1–10*	*11–20*	*21–30*	*31–40*	*41–50*	*51–60*	*61–70*	*Totals*
Over 60		1						1
56–60		1	1	1				3
51–54		2		2	2			6
46–50		3	9	6	1	1	1	21
41–45	1	7	13	9	9	1		40
36–40		7	15	11	2	1		36
31–35		2	4	2				8
Under 31				1				8
Totals	1	23	42	32	14	3	1	116

TABLE 2.—URINARY ESTROGEN AND SERUM CHOLESTEROL IN TOTAL GROUP OF 147 MALES

Urinary Estrogen Levels (μg./100 ml.)

SERUM CHOLESTEROL—mg./100 ml.	*1–10*	*11–20*	*21–30*	*31–40*	*41–50*	*51–60*	*61–70*
Over 350		1	5	8	4		
301–350		7	8	8	5	1	
276–300	1	2	11	4	5	2	1
251–275		8	9	6	2	1	
226–250		4	8	6	2		1
200–225		4	9	2			
Under 200		3	4	5			

serum cholesterol levels must generally be of the magnitude that also produces significant changes in secondary sex characteristics (Gertler, Hudson and Jost[4]). It has also been observed that in those areas of the world and in those individuals that may be more vulnerable to the development of clinical coronary artery disease.

Summary. In males of comparable age, race, ethnic origin, physical activity and cultural and dietary background, the pattern of 24-hour estrogenuria among the various somatotypes was similar. There was also no significant differences in the 24-hour estrogen excretion pattern between the "normal" males and those with clinical evidence of coronary atherosclerosis.

TABLE 3.—URINARY ESTROGENS AND SERUM CHOLESTEROL IN MALES WITH CLINICAL EVIDENCE OF CORONARY ARTERY DISEASE

SERUM CHOLESTEROL—mg./100 ml.	*Urinary Estrogen Levels (μg./100 ml.)*					
	11–20	*21–30*	*31–40*	*41–50*	*51–60*	*61–70*
Over 350		4	3			
301–350	2	2		3		
276–300		2			1	
251–275		1	3			
226–250	1	1				1
200–225	1	1	1			
Under 200		1	1			

races where coronary atherosclerosis is not so prevalent, the sex differences in clinical coronary artery disease are likewise not very striking (Lober[6]). For these reasons, the pattern of urinary estrogen excretion cannot be used as an aid in pre-selecting those

REFERENCES

1. **Bauld, U. S., Gioner, M. L.,** and **Milne, J. G.:** Canad. J. Biochem. & Physiol., **35,** 1277, 1957.
2. **Finkelstein, M.:** Acta endocrinol., **10,** 149, 1952.
3. **Gertler, M. M., Garn, S. M.,** and **White, P. D.:** J. Am. Med. Assn., **147,** 621, 1951.
4. **Gertler, M. M., Hudson, P. B.,** and **Jost, H.:** Geriatrics, **8,** 500, 1953.
5. **Gertler, M. M., Woodbury, M. A., Gottsch, L., White, P. D.,** and **Rusk, H. A.:** J. Am. Med. Assn., **170,** 149, 1959.
6. **Lober, P. H.:** A.M.A. Arch. Path., **55,** 357, 1953.
7. **Piel, A. C.:** Brit. Heart J., **17,** 319, 1955.
8. **Peck, R., Stamler, J., Rodbard, S.,** and **Katz, L. N.:** Circulation, **6,** 276, 1952.
9. **Sheldon, W. H.:** The Varieties of Human Physique. New York: Harper & Bros., 1940.
10. **Spain, D. M.,** and **Bradess, V. A.:** A.M.A. Arch. Int. Med., **100,** 228, 1957.
11. **Spain, D. M., Bradess, V. A.,** and **Huss, G.:** Ann. Int. Med., **38,** 254, 1953.
12. The Conference on Longitudinal Cardiovascular Studies: Brookline, Mass., 1957.
13. **Wuest, J. H., Jr., Dry, T. J.,** and **Edwards, J. E.:** Circulation, **7,** 801, 1953.

(Interlingua on page 620)

OBSERVATIONS ON THE USE OF NICOTINIC ACID TO INDUCE *IN VIVO* FIBRINOLYTIC ACTIVITY

By William L. Wilson, M.D.
ASSISTANT PROFESSOR OF MEDICINE, CHIEF, HEMATOLOGY AND CANCER CHEMOTHERAPY SECTION, HAHNEMANN MEDICAL COLLEGE AND HOSPITAL OF PHILADELPHIA

AND

George Fostiropoulos, M.D.
FELLOW IN HEMATOLOGY, DEPARTMENT OF MEDICINE, HAHNEMANN MEDICAL COLLEGE AND HOSPITAL OF PHILADELPHIA
PHILADELPHIA, PENNSYLVANIA

The present methods of anticoagulant therapy have proven beneficial in a variety of thromboembolic phenomena. However, the use of heparin or Dicumarol, or both, has one major drawback in that thrombi already formed are not lysed. For this reason a variety of methods to induce fibrinolysis have been proposed and are under investigation. The substances which are being utilized vary considerably in their composition and include active plasmin, proteolytic enzymes, direct activators of plasminogen, and indirect activators of plasminogen. A summation of these agents based on their composition and mode of action follows.

1. PROTEOLYTIC ENZYMES, PLASMIN AND PLASMINOGEN ACTIVATORS. This group consists of a variety of agents including trypsin, chymotrypsin, various preparations of nontoxic fungi (Stefanini and Marin[7]) and human or bovine plasmin. The plasmin preparations are activated by urokinase or streptokinase when human plasminogen is used or streptokinase bovine plasminogen is used (Bach *et al.*[1], Editorial[3], Sokal, Ambrus and Ambrus[6]). The intravenous administration of highly purified streptokinase has also been utilized for *in vivo* activation of the native plasminogen. Whereas the agents in this group will induce *in vivo* fibrinolysis, they have the disadvantage of being associated with side reactions which limit their being used in therapeutic concentrations. The therapeutic benefit of this group is under study but it appears that the injection of active plasmin may have limited usefulness because of its rapid inactivation by inhibitors normally found in the blood. Two important objections to agents in this group are the injection of a foreign protein with its associated dangers and the possibility of overactivation of plasmin resulting in proteolysis of fibrinogen and other plasma proteins.

2. ARTIFICIALLY PRODUCED HYPERPYREXIA. Artificially induced hyperpyrexia utilizing bacterial polysaccharides (Cochran, Whitney and Ware[2], von Kaulla[9], Meneghini[5]) will increase the fibrinolytic activity of the blood. Unfortunately, the hyperpyrexia is of such a degree that this method of inducing fibrinolysis would hardly be applicable to patients. Another disadvantage is that repetition of fever induction is not accompanied by an increase in the fibrinolytic activity.

3. MISCELLANEOUS NONPROTEIN AGENTS. There are a variety of nonprotein agents which if injected intravenously in sufficient concentration will induce increased fibrinolytic activity. These include epinephrine, procaine, irgapyrin, para-aminobenzoic acid and nicotinic acid. Of this group

only nicotinic acid has produced sufficient fibrinolytic activity to be clinically applicable in thromboembolic disorders.

This report is based on the observation of fibrinolytic activity following the administration of nicotinic acid. That intravenous nicotinic acid will induce fibrinolysis was first reported by Menegheni and Piccinini[4] who observed the lysis of recalcified plasma clots. Later Weiner, Redisch and Steele[10] repeated these observations but utilized coagulograms as well as lysis time of recalcified plasma clots to detect fibrinolysis. They observed that the maximum fibrinolytic activity occurred 10 to 15 minutes after intravenous administration. The side effect of "flushing" was observed in these patients when the time of administration was 4 minutes or less.

In this study our aims were: 1) to observe the fibrinolytic activity of intravenous and oral doses of nicotinic acid and nicotinamide; and 2) to determine whether nicotinic acid can be administered intravenously in such a manner as to induce fibrinolytic activity but avoid the profound "flush" that is usually observed.

Materials and Methods. Convalescent patients without hematological or hepatic disorders (the only exception being one patient with a portocaval shunt) were utilized for the study. In one group of individuals the effect of orally and intravenously administered nicotinic acid (10 mg. per ml.) in various doses was observed, as well as the effect of intravenous nicotinamide. In another group of individuals the nicotinic acid was administered as a solution containing 1 mg. per ml. in 5% glucose in distilled water over various periods of time. *In vitro* estimations of the fibrinolytic activity of the plasma as well as fibrinogen levels were determined at intervals during the administration. The latter method of administration was utilized in an attempt to eliminate or to avoid the "flush" and to maintain the fibrinolytic effect of the nicotinic acid. In all instances control fibrinolysis and fibrinogen estimations were performed before administration of the nicotinic acid. The recipients were closely observed for bleeding manifestations and blood pressure changes. For the *in vitro* estimation of the spontaneous fibrinolytic activity of the plasma we used a modification of the euglobulin fibrinolysis method of von Kaulla and Schultz[8]. The modification consists of precipitating the plasma euglobulins by a dilute acetic acid solution of pH 5.3 and then resuspending the precipitate in phosphate buffer at a pH of 7.4. The resuspended euglobulins are then clotted with thrombin and incubated at 37° C. in a water bath. A euglobulin lysis time of 5 to 8 hours is normal at this laboratory. Fibrinogen levels were determined by the standard digestion method with color development by Folin Wu Ciocaltoux reagent. The solutions were then read against a blank in a model B Beckman spectrophotometer at 560 mu.

Results. Table 1 illustrates the results of nicotinic acid and nicotinamide administration in 9 convalescent patients.

The intravenous injection of 100 mg. of nicotinic acid over a period of 3 to 4 minutes was always followed by a marked increase in the spontaneous fibrinolytic activity of the plasma in 5 to 10 minutes. The maximum activity was at 10 to 15 minutes but had disappeared at 30 minutes. This is apparently due to the rapid inactivation of the excess plasmin by inhibitors. In case No. 8, the patient received 7 intravenous doses of 100 mg. of nicotinic acid at 12-hour intervals. The fibrinolytic activity was increased after the 7th dose although not to the level observed after the first injection. In case No. 3, 200 mg. of intravenous nicotinic acid increased the fibrinolytic activity only to the same degree and duration as did an intravenous dose of 100 mg.

Case 9 is a patient with portal cirrhosis and a portocaval shunt. In this instance an oral dose of 100 mg. of nicotinic acid caused an increase in the fibrinolytic activity. Repeat administration by the intravenous route of 50 mg. of nicotinic acid the following day, again re-

TABLE 1.—EFFECT OF NICOTINIC ACID AND NICOTINAMIDE ON BLOOD FIBRINOGEN LEVELS AND FIBRINOLYTIC ACTIVITY

			Fibrinogen mg./100 ml. at indicated time						*Euglobulin Lysis Time in Minutes*						*Flush*	
N	*Medication and Dose**	*Route of Administration*	*Control*	*5 m*	*10 m*	*20 m*	*30 m*	*45 m*	*Control m*	*5 m*	*10 m*	*20 m*	*30 m*	*45 m*	*Degree*	*Time in Minutes*
1	100 mg. NA	I. V.	450	430	375				420	20	15	420	420		++++	15
2	100 mg. NA	I. V.	680	583	580	430			510	180	120	300	480		++	15
3	200 mg. NA	I. V.	640	605	580	590	580		480	200	150	480	480		++++	10
4	50 mg. NA	I. V.	310	310	315	300	300		480	270	240	450	480		+	5
5	50 mg. N	I. V.	385	380	390	390	385		420	420	420	420	420		—	—
6	100 mg. N	I. V.	390	390	390	390	390		390	390	390	450	450		—	—
7	100 mg. NA	P. O.	305					310	435					430	++	10
8†	100 mg. NA	I. V.	310		260	282			340		60	310			++++	15
	100 mg. NA	I. V.	320		315	308			300		150	285			++++	5

			Fibrogen mg./100 ml.						*Euglobulin Lysis Time in Minutes.*					
			Control	*15 m*	*30 m*	*45 m*	*60 m*	*120 m*	*Control*	*15 m*	*30 m*	*45 m*	*60 m*	*120 m*
9‡	100 mg. NA	P. O.	230	180	180	155	140		285	280	45	80	220	
	50 mg. given over 30 min.	I. V.	220	165	165	175	172	170	300	40	45	70	115	195

*NA indicates nicotinic acid. N indicates nicotinamide.
†The results for the first and the 7th administration of 100 mg. I. V. every 12 hours are given.
‡This patient had a portocaval shunt.

sulted in increased fibrinolytic activity. This supports the observations of Weiner, Redisch and Steele[10] that oral nicotinic acid in patients with a portocaval shunt will induce increased fibrinolytic activity. However, the fact that within 24 hours the administration of nicotinic acid again resulted in increased fibrinolytic activity is not in agreement with the observations of Weiner, Redisch and Steele[10].

The fibrinogen levels remained within normal limits even though a decrease was noted in several instances. In all instances the individuals felt the"flush" associated with nicotinic acid administration, which appeared approximately 2 to 3 minutes after the start of administration and lasted approximately 10 to 15 minutes. It consisted of a burning feeling that involved first the face and the abdomen and then spread over the trunk and the extremities. The intensity of the "flush" was graded from 1 to 4 plus.

One plus was a slight well tolerated warm feeling around the face. Two plus was a burning sensation of the face and the neck accompanied by slight nausea. When the burning was also felt on the trunk and the nausea was more intense, the flush was graded 3 plus. The 4 plus designation was given when the burning was very intense and spread over the entire body and extremities, and was associated with intense nausea. The nausea was not accompanied by vomiting.

The "flush" usually lasted 10 to 15 minutes and was followed by a feeling of weakness. No instances of bleeding phenomena were observed and the tourniquet test was always negative. The systolic blood pressure fell 10 to 20 mg. of Hg in the patients who received intravenous nicotinic acid, but this fall was not correlated with the severity of "flush." In the second group of 8 patients, the intravenous infusion of nicotinic acid was diluted to 1 mg. per ml. with 5% glucose in distilled water. The data from this series of patients . is shown in Table 2. Two cases received 200 mg. of nicotinic acid in 200 ml. of 5% glucose over a period of 1 hour. Plasma euglobulin lysis times and fibrinogen determinations were done before and at 15 minutes, 30 minutes, 1 hour and 2 hours after the beginning of the infusion. In both cases the specimen at 15 minutes showed markedly increased fibrinolytic activity with lysis times of 1 hour 30 minutes and 2 hours 15 minutes. The control times of these individuals were 7 hours and 6 hours respectively.

However, in both cases the subsequent specimens showed disappearance of the activation. Two other cases received 100 mg. nicotinic acid in 100 ml. of 5% glucose in distilled water over a period of 30 minutes. The maximum effect was again at 15 minutes and there was a return to control levels after 30 minutes. The fibrinogen levels in these patients remained within normal limits and close to the control levels. The side effects were insignificant in this group. There was a slight "warm" feeling which began 2 or 3 minutes after the start of the infusion and lasted for 10 or 15 minutes. At the time of peak fibrinolytic activity they had no complaints. The blood pressure remained unchanged. In the subsequent 4 cases (5, 6, 7, 8 and Table 2) repeat doses of nicotinic acid in 5% glucose in distilled water were followed by increased fibrinolytic activity. Initially 100 mg. of nicotinic acid in 100 ml. of 5% glucose was given over a period of 20 minutes. This was followed by 5% glucose in distilled water for the next 20 minutes and then 100 mg. nicotinic acid in 100 ml. of 5% glucose for the third 20-minute period. Euglobulin lysis tests and fibrinogen determinations were determined before

TABLE 2.—EFFECT OF INTRAVENOUS NICOTINIC ACID IN 5% GLUCOSE ON BLOOD FIBRINOGEN LEVELS AND FIBRINOLYTIC ACTIVITY.

N P	Medication and Dose*	Method of Administration	Fibrinogen mg./100 ml. at indicated time.							Euglobulin Lysis Time in Minutes							Flush	
			Control	15 m	30 m	60 m	90 m	120 m		Control	15 m	30 m	60 m	90 m	120 m		Degree	Time in Minutes
1	200 mg. N	1 hour	275	275	189	242	236	240		420	90	420	420	420	420		+	5
2	200 mg. N	1 hour	310	310	310	312	300	315		360	135	360	370	360	360		+	10
3	100 mg. N	30 minutes	292	258	260					360	20	240					+	5
4	100 mg. N	30 minutes	260	260		258	258			330	150	300	310	310			+	5
			Control	10 m	20 m	30 m	40 m	50 m	60 m	Control	10 m	20 m	30 m	40 m	50 m	60 m		
5	100 mg. N	20 minutes	510	415	412					370	20	60					+	10
	5% Glucose	20 minutes				415	420						360	360			—	—
	100 mg. N	20 minutes						422	440						190	380	—	—
6	100 mg. N	20 minutes	358	358	358					450	240	420					—	—
	5% Glucose	20 minutes				305	315						450	450			—	—
	100 mg. N	20 minutes						330	345						270	420	—	—
7	100 mg. N	20 minutes	275	230	265					390	45	120					—	—
	5% Glucose	20 minutes				265	272						370	370			+	10
	100 mg. N	20 minutes						270	282						120	340	—	—
8	100 mg. N	20 minutes	520	503	525					430	120	300					—	—
	5% Glucose	20 minutes				510	512						400	405			—	—
	100 mg. N	20 minutes						500	512						140	345	—	—

*The nicotinic acid was diluted with 5% glucose in distilled water to a concentration of 1.0 mg. nicotinic acid/ml. of solution.

and every 10 minutes for a period of 1 hour. In all 4 cases the specimen drawn 10 minutes after the infusion was started showed increased fibrinolytic activity with euglobulin lysis times of 45 minutes to 2 hours with normal controls of 6 to 7 hours. In the 20-minute specimen the activity had decreased or had reached the control time. In the next 2 specimens at 30 and 40 minutes when only glucose was running, there was no increased activity. However, in the last two specimens, at 50 and 60 minutes, when the nicotinic acid-glucose solution was being repeated, the fibrinolytic activity was again markedly increased. The euglobulin lysis times in the 50-minute specimen were much shorter than the control specimens and in one case (no. 7) the same as the 10-minute specimen. There was a return to the control time in the 60-minute specimens with the slow rate of administration; the vasomotor side effects were not manifested. Only 2 patients experienced 1+ "flush" for the first 10 minutes during the first administration of nicotinic acid. Fibrinogen levels did not show a significant change.

Discussion. The fibrinolytic effect of nicotinic acid is apparent. Meneghini and Piccinini[4], who first observed this activity, felt that there was only a moderate increase in activity. However, they used the less sensitive method of lysis of recalcified plasma clot to study fibrinolytic activity. By utilizing the thrombin precipitated euglobulin clots we were able to eliminate the antifibrinolytic action of the antiplasmins which are present primarily in the albumin fraction. The maximum effect in our experiments was observed 10 to 15 minutes after the start of the administration which is in agreement with the work of Weiner *et al.*[10,11]. However, the plasmin activity disappeared rapidly within 30 minutes.. This is most likely due to inactivation by antiplasmin. Oral nicotinic acid in a single dose of 100 mg. was not followed by any fibrinolytic response but was associated with a 2+ "flush," except as noted in the patient with a portocaval shunt. The observation that oral nicotinic acid in a patient with a portocaval shunt results in an increased plasmin activity tends to incriminate the liver as the site where the nicotinic acid loses its ability to stimulate plasmin activity. There was no fibrinolytic response to the intravenous administration of nicotinamide which confirms the work of the other observers. Meneghini and Piccinini[4] found nicotinic acid alcohol (Romicol) to be without activity.

By utilizing a slow intravenous infusion of nicotinic acid diluted to 1 mg. per ml. in 5% glucose, the same degree of fibrinolysis as with a single intravenous dose was obtained. However, the former method of administration avoids the "flush" and nausea which accompany a single injection given over a period of 4 minutes. The degree and the duration of the activation were of the same magnitude. Repeat infusions after a short interval during which time the activity disappeared, were accompanied by reactivation of approximately the same degree. This is in contrast with the negative response obtained by Weiner, DeCrinis and Redisch[11] to repeat injections.

At this time very little is known about the mechanism by which nicotinic acid activates plasminogen. It is not a direct activator as the addition of nicotinic acid to blood *in vitro* causes no increase in fibrinolytic activity. The activity is undoubtedly associated with a normal activator which is released by the nicotinic acid. It is probably not dependent on the mechanism that produces the "flush" that is

observed with intravenous and oral doses. This is substantiated by the fact that oral doses in normal individuals cause a "flush" but no increased fibrinolytic activity whereas an oral dose in patients with a portocaval shunt will result in the "flush" as well as increased fibrinolytic activity.

Summary. These observations support the work of Meneghini and Piccinini[4] and Weiner *et al.*[10,11] in that intravenous nicotinic acid will activate plasminogen. However, in our studies we were able repeatedly to activate plasminogen which is contrary to the work of Weiner, DeCrinis and Redisch[11]. The mechanism for activation of plasminogen is probably not dependent on the same mechanism responsible for the production of the "flush." We have also observed that nicotinic acid can be given in a slow intravenous infusion with activation of the plasminogen and a minimum activation of the flushing mechanism. Further studies as to the mechanism of action are indicated.

REFERENCES

1. **Bach, N., Ambrus, J. J., Golstein, S.,** and **Harrison, J. W. E.:** Circ. Res., **4**, 440, 1956.
2. **Cochran, B., Jr., Whitney, E. B.,** and **Ware, A. G.:** Pharmaceutica Acta Helvetiae., **33**, 719, 1958.
3. Editorial: Lancet, **2**, 624, 1958.
4. **Meneghini, P.,** and **Piccinini, F.:** Arch. E. Maragliano, **14**, 69, 1958.
5. **Meneghini, P.:** Acta haematologica., **19**, 65, 1958.
6. **Sokal, J. E., Ambrus, J. L.,** and **Ambrus, C. M.:** J. Am. Med. Assn., **168**, 1314, 1958.
7. **Stefanini, M.,** and **Marin, H.:** Proc. Soc. Exper. Biol. & Med., **99**, 504, 1958.
8. **von Kaulla, K. N.,** and **Schultz, R. Z.:** Am. J. Clin. Path., **29**, 104, 1958.
9. **von Kaulla, K. N.:** Pharmaceutica Acta Helvetiae., **33**, 727, 1958.
10. **Weiner, M., Redisch, W.,** and **Steele, M.:** Proc. Soc. Exper. Biol. & Med., **98**, 755, 1958.
11. **Weiner, M., DeCrinis, K.,** and **Redisch, W.:** Fed. Proc., **18**, 168, 1959.

SUMMARIO IN INTERLINGUA

Observationes in le Uso de Acido Nicotinic pro Inducer Activitate Fibrinolytic in Vivo

Le observationes hic reportate corrobora le conclusion de Meneghine e Piccinini[4] e de Weiner *et al.*[10,11], a saper que acido nicotinic per via intravenose effectua un activation de plasminogeno. Per contrasto con le observation reportate per Weiner, DeCrinis, e Redisch[11], nos trovava que le activation de plasminogeno pote esser effectuate repetitemente per le methodo in question. Il es probabile que le mechanismo del activation de plasminogeno non depende del mechanismo que produce le fluxion notate post le injection intravenose de acido nicotinic. Nos ha constatate que acido nicotinic pote esser administrate per un lente infusion intravenose, resultante in le mesme activation de plasminogeno sed in un activation minimal del mechanismo de fluxion. Studios additional relative al mechanismos interessate in iste phenomenos es indicate.

SERUM LEUCINE AMINOPEPTIDASE ACTIVITY: FINDINGS IN CARCINOMA OF THE PANCREAS, PREGNANCY AND OTHER DISORDERS*

By Herbert E. Arst, M.D.
RESIDENT IN MEDICINE, UNIVERSITY OF KANSAS MEDICAL CENTER

Robert T. Manning, M.D.
INSTRUCTOR IN MEDICINE, UNIVERSITY OF KANSAS SCHOOL OF MEDICINE

AND

Mahlon Delp, M.D.
PROFESSOR OF MEDICINE, UNIVERSITY OF KANSAS SCHOOL OF MEDICINE

(From the Department of Medicine, University of Kansas Medical Center, Kansas City, Kansas)

Leucine aminopeptidase (LAP) is a proteolytic enzyme needed in the terminal digestion of L-leucyl peptides, which occurs principally in the small intestinal mucosa and in pancreatic extracts. It has been found in most human tissues, animals, plants and microorganisms (Millonig[13], Smith[18,19], Thomas[21]), and has been histochemically demonstrated in the stroma of cancers (Burstone[5]). The function of this enzyme in the blood is not known.

The recent work of Rutenburg, Goldbarg and Pineda[17] has stimulated considerable interest concerning the diagnostic importance of serum LAP in patients with carcinoma of the pancreas. Since this condition is notoriously difficult to diagnose clinically, such a test would be of great aid in differentiating it from relatively benign disorders such as choledocholithiasis or viral hepatitis. These authors stated that serum LAP activity was markedly elevated in all of their 14 patients with carcinoma of the pancreas. They implied that such marked elevation occurs in no other condition and is, therefore, highly suggestive of pancreatic carcinoma. They stated that "Assays of leucine aminopeptidase are especially definitive, when normal, in ruling out cancer of the head of the pancreas."

They also noted that LAP values are increased in pregnancy, as did Green *et al.*[10]. Neither of these reports stated the period of gestation in which elevations occur nor the degree of increase. Rutenburg, Goldbarg and Pineda[17] reported also that LAP was regularly demonstrated in spinal fluid, gastric juice, bile, duodenal secretions, pleural and peritoneal fluids. The levels of the enzyme present in these fluids were not given.

In an attempt to confirm these findings, we studied the serum activity of leucine aminopeptidase in patients with various diseases and in pregnancy.

Materials and Methods. The reactions carried out in the determination of leucine aminopeptidase activity in the serum or other body fluids are given in Fig. 1. The enzymatic hydrolysis of L-leucyl B-naphthylamide is involved, and the colorimetric determination

*Supported by Grant No. A–1709, National Institute of Arthritis and Metabolism National Institutes of Health, United States Public Health Service.

of one of the products, B-naphthylamine, is performed by modification of the Bratton-Marshall reaction[4]. The modifications employed are well outlined by Goldbarg and Rutenburg[9]. These authors found that, in certain instances, significant protein binding with B-naphthylamine may result in an apparent decreased LAP activity. This phenomenon did not occur under the conditions used. No urinary assays were performed. Kinetic studies were made and were found to agree closely with the results of others (Goldbarg[9], Green *et al.*[10]).

ml. of supernatant is then transferred to a colorimetric tube and 1.0 ml. of 0.1% sodium nitrite is added. After at least a 3-minute wait, 1.0 ml. of 0.5% ammonium sulfamate is added to destroy excess sodium nitrite, followed 2 minutes later by the addition of 2.0 ml. of naphthylene ethylene diamine dihydrochloride (0.5 mg. per ml. in 95% ethyl alcohol). Exactly 15 minutes later, 5 ml. of distilled water is added, the contents mixed by inversion and the blue color obtained read against the blank at 560 m. A standard calibration curve is used to calcu-

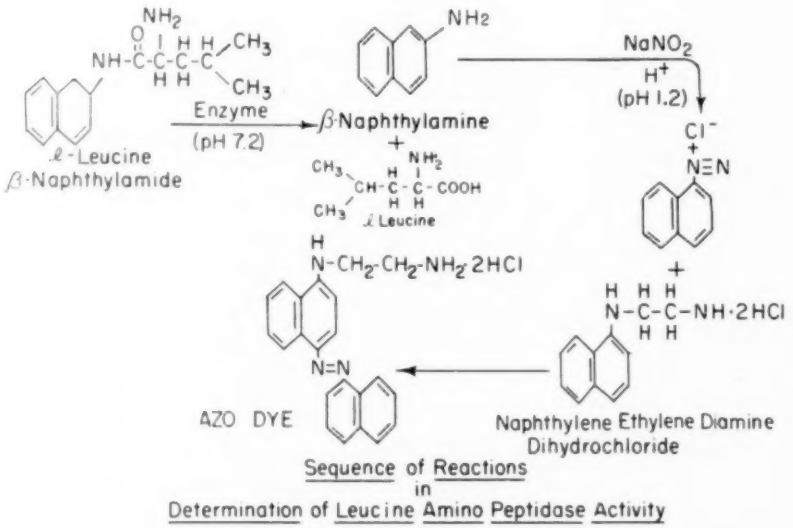


Fig. 1

The procedure for testing is outlined in Fig. 2. A blank is prepared by using 1.0 ml. of distilled water and is run in a like manner with the specimen to be measured. One-tenth milliliter of material (serum or other fluid) is required and is diluted with 0.9 ml. of distilled water. One milliliter of buffered substrate* (concentration 2 μM. per ml.; pH 7.2) is added by pipet and the reaction allowed to proceed at 37° C. for 30 minutes. At the end of that time, the reaction is stopped abruptly by the addition of 1.0 ml. of 1.0 N perchloric acid. The tubes are centrifuged for 10 minutes at 3000 rpm.; 1.0 ml. of supernatant is then transferred to a colorimetric tube and 1.0 ml. of 0.1% sodium nitrite is added. After at least a 3-minute wait, 1.0 ml. of 0.5% ammonium sulfamate is added to destroy excess sodium nitrite, followed 2 minutes later by the addition of 2.0 ml. of naphthylene ethylene diamine dihydrochloride (0.5 mg. per ml. in 95% ethyl alcohol). Exactly 15 minutes later, 5 ml. of distilled water is added, the contents mixed by inversion and the blue color obtained read against the blank at 560 m. A standard calibration curve is used to calculate the units, corrected for use of only 1 ml. of supernate. The calibration curve is a linear one, up to 0.3 M per tube, and is prepared by using known amounts of B-naphthylamine hydrochloride. Accuracy on replicate determinations was within ± 4%. A Universal Coleman spectrophotometer was used in this study. Determinations giving optical densities above 1.2 were repeated, using lesser amounts of serum.

A clinical unit of LAP activity is defined as the formation of .001 micromole of B-naphthylamine in 30 minutes at 37° C. at a substrate concentration of 1 μM per ml.

*To prepare buffered substrate of leucine B-naphthylamide (4 μM. per ml.), 118 mg. is dissolved in 100 ml. of distilled water. Thirty-nine milliliters of 0.2 M monosodium phosphate and 61 ml. of 0.2 M disodium phosphate are added, making a total volume of 200 ml.

at pH 7.2. Thus, 100 clinical units is equivalent to the hydrolysis of 0.1 μM. of substrate. It should be pointed out that the units given by Goldbarg and Rutenburg[9] are direct readings from the Klett colorimeter and thus differ from those reported here. The number of micromoles formed, however, should be the same in any laboratory under the above conditions.

Rutenburg, Goldbarg and Pineda[17] found that hemolysis had no effect on LAP activity in the serum; however, we found that complete hemolysis increases serum activity as much as three and one-half times. Other investigators (Adams, McFadden and Smith[1], Stern *et al.*[20]) found that peptidase activity in the formed elements of the blood exceed by far that of serum. It was reported that a volume of packed red cells gives 100 times the activity of peptidase as would an equal volume of serum. Packed white cells have 500 times the serum values. For this reason, hemolyzed sera were rejected for analysis even though slight hemolysis did not alter the LAP activity.

For assay, blood was drawn in the fasting state, allowed to clot and the serum removed and centrifuged a second time. Likewise, spinal fluid, bile, saliva, gastric juice, pleural and peritoneal fluids were doubly centrifuged to remove as much particulate material as possible prior to assay.

The effect of temperature on serum LAP activity was measured. The mean value of 10 normal sera at each of the temperatures was taken to calculate the percentages. It appears that there is no change in activity after storage at 4° C. for a 5-day period. However, at the end of 3 weeks, a loss of 15% activity was noted. At room temperature, there was a loss of 15% activity after only 2 days, and 18% at the end of 3 weeks. Little change in activity could be detected from the 3rd to the 6th weeks.

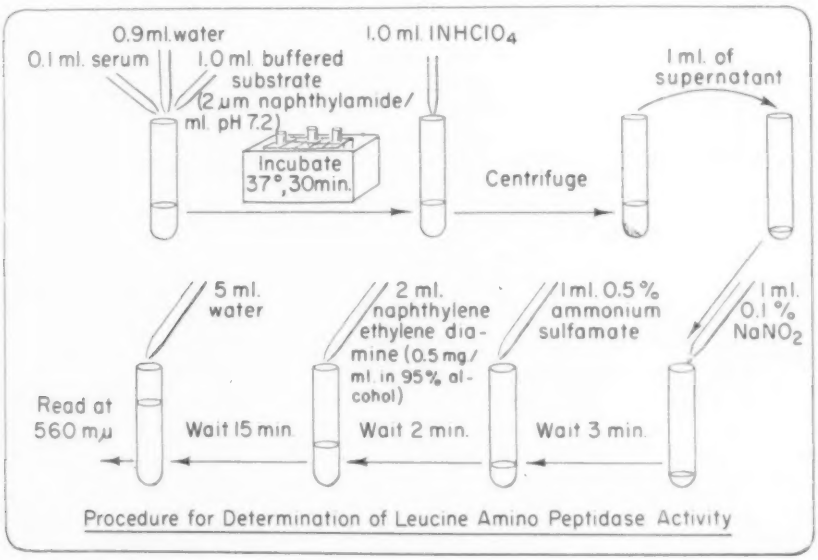

0.9 ml. water
0.1 ml. serum
1.0 ml. buffered substrate (2 μm naphthylamide/ml. pH 7.2)
Incubate 37°, 30 min.
1.0 ml. $INHClO_4$
Centrifuge
1 ml. of supernatant
5 ml. water
2 ml. naphthylene ethylene diamine (0.5 mg./ml. in 95% alcohol)
1 ml. 0.5% ammonium sulfamate
1 ml. 0.1% $NaNO_2$
Read at 560 mμ
Wait 15 min.
Wait 2 min.
Wait 3 min.
Procedure for Determination of Leucine Amino Peptidase Activity

Fig. 2

Results. NORMAL RANGE. A total of 70 healthy persons were utilized to determine the normal range. This group was divided equally between the sexes, as depicted in Table 1. Using twice the standard deviation, the normal range for the total group was from 52 to 144 or, in round figures, 50 to 150 units. For purposes of discussion here, the upper limit of normal will be taken at 150 units. One will note that the mean for the female group is approximately three-fourths that found for

TABLE 1.—THE NORMAL RANGE

Groups	*Number of Individuals*	*Range*	*Mean*	*S.D.*	*Mean + 2 S.D.*	*Normal Range*
Total	70	58–169	98	23	52–144	50–150
Males	35	80–169	111	17	77–145	75–150
Females	35	58–135	85	22	41–129	40–130

Table 2.—CONDITIONS IN WHICH NORMAL LAP ACTIVITY WAS FOUND

	No. of Cases		*No. of Cases*
Carcinoma of the Lung	18*	Neurofibromatosis	1
Carcinoma of the Breast with Liver Metastases	1	Plantar Wart	1
Carcinoma of the Esophagus	1	Hereditary Telangiectasia	1
Carcinoma of the Rectum	3	Urticaria pigmentosa	1
Carcinoma of the Bladder	3	Hypersensitivity Reaction	1
Carcinoma of the Ovary	3	Exfoliative Dermatitis	1
Carcinoma of the Endometrium	1	Duodenal Ulcer (active)	14
Carcinoma of the Kidney with Lung Metastases	2	Irritable Bowel Syndrome	30
Pseudomyxoma peritonaei	1	Diverticulosis	4
Nasopharyngeal Carcinoma	1†	Polyp of Colon	2
Malignant Thymoma	1	Gastroenteritis	1
Seminoma	1	Small Bowel Obstruction	1
Multiple Myeloma	3	Benign Gastric Ulcer	1
Hodgkin's Disease	4	Chronic Pancreatitis	8
Pancytopenia	2	Pancreatic Pseudocyst	1
Pernicious Anemia	1	Pancreatic Insufficiency	2
Thrombotic Thrombocytopenia	1	Partial Pancreatectomy	1
Aplastic Anemia	1	Biliary Cirrhosis	2
Acute Acquired Hemolytic Anemia	1	Chronic Brain Syndrome	1
Anaphylactoid Purpura	1	Visceral Neuropathy	1
Polycythemia Vera	1	Barbiturate Intoxication	1
Scleroderma	1	Aseptic Meningitis	1
Polyserositis	1	Cerebellar Disease	1
Hypertensive Vascular Disease	9	Cerebral Vascular Accident	2
Peripheral Vascular Disease	6	Cerebral Atrophy	1
Rheumatic Heart Disease	3	Renal Stone	1
Myocardial Infarction (1 week)	4	Hypoplastic Kidney	1
Idiopathic Myocarditis	1	Nephrotic Syndrome	1
Cor Pulmonale	1	Lumbosacral Strain	1
Status Asthmaticus	1	Paget's Disease	1
Pneumonia	1	Osteoarthritis	1
Pulmonary Infarction	1	Osteoporosis	1
Influenza	1	Gout	1
Uterine Fibroids	1	Functional Hypoglycemia	1
Menorrhagia	1	Achromegaly	1
Herpes Simplex	1	Hyperaldosteronism	1
		Cushing's Syndrome	1
		Addison's Disease	1
		Acute Intermittent Porphyrinuria	1
		Total	178

*One with metastasis to liver.

†Cerebral metastasis.

males. Rutenburg, Goldbarg and Pineda[17] found a greater difference; their evaluation showed the female mean to be approximately one-half that of the male.

PATIENT MATERIAL. Six-hundred forty-four sera determinations were made on 497 patients. The data on these subjects has been divided into 4 major groups. The diagnosis of cancer in most cases was proven histologically, either at the time of surgery or at necropsy.

Table 2 shows conditions in which normal LAP activity was found. One-hundred seventy-eight patients are represented. Conditions in which both normal and elevated LAP activity was found are represented by 136 patients in Table 3. Note that, of 16 patients with proven carcinoma of the head of the pancreas, 4 had normal serum LAP activity. Of these 4 with normal values, 2 were jaundiced and 2 were not. In the remaining 3 (total of 19 patients), the diagnosis was strongly suspected; however, at the time of this writing, these patients were too ill to undergo surgery.

It is of interest to observe that active parenchymal liver disease, such as viral hepatitis, frequently produces abnormal values, whereas stable diffuse hepatic fibrosis was associated with normal values in approximately one-half of the patients. The abnormal LAP levels for the 4 patients with carcinoma of the colon and liver metastases were 567, 360, 350 and 242. Those patients with carcinoma of the stomach and hepatic spread had levels of 232, 228, 127 and 48. In the patient with chronic cholecystitis and cholelithiasis, the LAP value was only slightly elevated.

Conditions in which elevated LAP values were found are shown in Table 4, representing 25 patients. Twelve patients with proven choledocholithiasis showed elevations in every case. All 4 patients with acute pancreatitis showed abnormal levels of the enzyme on admission. A young girl with subacute bacterial endocarditis on 3 separate hospital admissions had levels of 452, 180 and 158 LAP units. The patient with an acute posterior myocardial infarction had daily serum GOT and LAP determinations revealing, however, no elevation of either until the 5th day, at which time she developed congestive heart failure. Two days later, a peak rise of 119 GOT units and 267 LAP units occurred, suggesting that the enzyme elevations

TABLE 3.—CONDITIONS IN WHICH NORMAL AND ELEVATED LAP ACTIVITY WAS FOUND

Condition	*Normal*	*Elevated*
Carcinoma of Prostate	4°	1
Carcinoma of the Stomach	9†	2‡
Carcinoma of the Colon with Liver Metastasis	3	4
Carcinoma of the Pancreas	4	15§
Chronic Cholecystitis and Cholelithiasis	6	1
Viral Hepatitis	3	18
Diffuse Hepatic Fibrosis	8	7‖
"Fatty Liver"	1	1
Subacute Pancreatitis	1	2
Esophageal Hiatus Hernia	3	1
Diabetes	6¶	–
Leukemia	7	2
Lymphosarcoma	1	1
Rheumatoid Arthritis (active)	4	1
Disseminated Lupus Erythematosus	2	1
Congestive Heart Failure	12	2
Sickle Cell Disease	1	1°°
Subtotals	75	61
Total Cases	136	

°Three with bone metastasis.
†Two with liver metastasis.
‡Two with liver metastasis.
§Three highly suspected.
‖One with congestive heart failure.
¶Two in acidosis
°°With pulmonary infarction.

came from the congested liver. Normal levels of both enzymes were reached by the 9th day and remained so thereafter.

The graph in Fig. 3 represents values from 128 healthy pregnant subjects, chosen at random from the prenatal outpatient clinic and delivery room. The shaded area represents the range of values found in each month of gestation, and the solid line indicates the corresponding mean. One will note that, in the first trimester (represented by 16 patients), normal values were obtained in almost every case. In the second trimester (38 patients), most values were in the normal range except for the latter part of this period. In the third trimester (46 patients), almost all values were high.

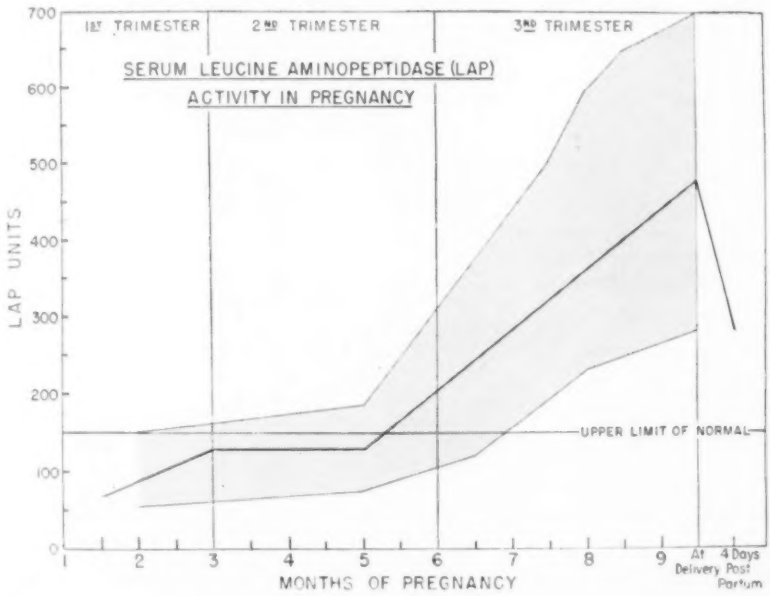


Fig. 3

TABLE 4.—CONDITIONS IN WHICH ELEVATED LAP ACTIVITY WAS FOUND

Condition	*No. of Cases*
Acute Pancreatitis	4
Choledocholithiasis	12
"Cardiac Cirrhosis"	2
Ulcerative Colitis	1
Carcinoma of Cystic Duct	1
Carcinoma Ampulla of Vater	1
Hepatoma	1
Acute Thyroiditis	1
Thalassemia major	1
Subacute Bacterial Endocarditis	1
Total Cases	25

At the time of delivery, 28 persons showed an average value of nearly 500 units with a drop to almost one-half this level 4 days following delivery. Further follow-up determinations were not possible.

Glutamic oxalacetic transaminase (GOT) activity was measured by the colorimetric method of Reitman and Frankel[16] in each pregnant patient where high LAP levels were obtained. Four showed elevated GOT activity. Three of these abnormal values were obtained at the time of delivery and

1 at 5 months' gestation. Of the 3 patients, 2 had preeclampsia (GOT 172 and 68; LAP 850 and 910 respectively). The other patient had a prolonged labor with postpartum hemorrhage without shock (GOT 95 and LAP 860). A 4th patient (not included in the graph) was found to have a "missed" abortion for a probable duration of 2 months prior to her GOT and LAP determinations (GOT 52 and LAP 610), which were obtained at 5 months' gestation. Two weeks later, the patient aborted. One will note that a LAP elevation of this degree for this period of time is far greater than would be expected. It was for this reason that she was not represented in the graph.

In Table 5, the LAP values found in patients with disorders of the biliary-pancreatic system have been grouped for purposes of comparison. The 4 normal values found in patients with carcinoma of the pancreas are again noted. The elevations noted in those patients with choledocholithiasis are compared with those 15 subjects with pancreatic carcinoma showing abnormal values. The presence of liver metastasis or severity of icterus did not correlate well with the degree of LAP activity in the serum of these patients. Persons with pancreatic insufficiency or partial pancreatectomy did not demonstrate abnormally low levels of this enzyme.

Table 6 represents LAP values in patients with disorders of the liver, excluding those involving the biliary-pancreatic system. It is interesting to note that active hepatic disease, such as viral hepatitis, resulted in levels relatively higher than those seen in more stable conditions such as diffuse hepatic fibrosis. Patients with decompensated cirrhosis tended to have higher levels than those whose disease was relatively quiescent. LAP determinations on patients with viral hepatitis were made between 1 and 3 weeks from the onset of jaundice. No correlation could be made between the duration or severity of jaundice and the degree of LAP activity.

Table 7 shows the LAP values found in various body fluids of 47 patients. Simultaneously with the collection of these fluids, blood samples were obtained. Bile was collected from draining T-tubes in 8 patients. LAP determinations on the collected specimens were made in an identical manner as

TABLE 5.—LAP VALUES IN DISORDERS OF THE BILIARY-PANCREATIC SYSTEM

Pancreatitis: Acute	290°, 277°, 219, 182
Subacute	278, 219, 110
Chronic	142, 135, 117, 117, 109, 91, 90, 68
Pancreatic Insufficiency	105, 72
Partial Pancreatectomy	115
Pseudocyst of Pancreas	111
Carcinoma of Pancreas	710, 505, 447†, 430†, 410, 400,
	380, 373, 360†, 358, 350, 310,
	260, 225, 175, 138, 100, 90, 84
Carcinoma Ampulla Vater	313
Carcinoma Cystic Duct	224
Cholecystitis and Cholelithiasis	154, 145, 132, 121, 111, 87, 79
Choledocholithiasis	366, 361, 343, 276, 262, 245, 230,
	228, 211, 196, 190, 168

°With high amylase.
†Highly suspect, not proven.

that for serum. The values for bile ranged from 108 to 976 units (mean 258). Using the mean values of these groups for purposes of calculation, serum contains approximately one-half the LAP activity of bile, but no individual correlation could be made when comparing blood and bile values of the enzyme.

Four samples of ascitic fluid were taken simultaneously with blood. The values from 2 patients with Laennec's cirrhosis, 1 patient with carcinoma of the ovary and 1 with hepatoma are shown. LAP determinations made from the cerebral spinal fluid of 20 patients with various neurological disorders showed no activity. We could not demonstrate the presence of this enzyme in the gastric juice from 10 fasting patients whose serum values were normal. Two saliva samples showed no activity. A secretin test was done on a patient with suspected carcinoma of the pancreas (serum LAP 447 units). No enzymatic activity could be detected prior to the test; however, following the administration of secretin, an activity of 54 units was obtained. Prior to injection of secretin, no LAP

TABLE 6.—LAP VALUES IN DISEASES OF THE LIVER

"Cardiac Cirrhosis"	200, 169
Biliary Cirrhosis (stable)	100, 98
Diffuse Hepatic Fibrosis	283, 254, 214, 207, 181, 165, 158, 146, 128, 108, 90, 72, 68, 67, 65
"Fatty Liver"	200, 87
Viral Hepatitis	717, 365, 360, 349, 275, 256, 235, 219, 215, 210, 194, 192, 183, 181, 175, 165, 159, 153, 122, 118, 85
Hepatoma	255

TABLE 7.—LAP VALUES IN VARIOUS BODY FLUIDS

Diagnosis	*Serum*	*Bile*	*Ascitic*	*Pleural*
Choledocholithiasis	211	976		
	262	575		
	343	112		
	245	108		
Viral Hepatitis	215	219		
Carcinoma of Pancreas	505	700		
Carcinoma of Ampulla Vater	313	146		
Carcinoma of Cystic Duct	224	395		
Laënnec's Cirrhosis	282		80	
	210		28	
Carcinoma of Ovary	92		59	
Hepatoma	255		10	
Myocardial Insufficiency	133			42

Sample	*No. of Cases*	*LAP Activity*
Cerebral Spinal Fluid	20	none
Gastric Juice	10	none
Saliva	2	none
Duodenal Juice* before Secretin	1	none
Duodenal Juice* after Secretin	1	54

*Diagnosis—Carcinoma of the pancreas

activity could be detected in this patient's gastric fluid.

Discussion. From the data presented, it appears that normal LAP values are found in a wide variety of malignant, hematological, cardiovascular, neurological, gastrointestinal, renal, dermatological and infectious disorders. However, almost any condition which affects the liver may produce abnormal serum levels of the enzyme. Rutenburg, Goldbarg and Pineda[17] found moderate elevations of serum LAP in patients with primary hepatic diseases such as viral hepatitis, cirrhosis and hepatoma; low-grade transient elevations in patients with acute pancreatitis and choledocholithiasis; and normal levels in patients with carcinoma not involving the hepato-biliary-pancreatic system. They also found that chronic cholecystitis and chronic pancreatitis, as well as malignant conditions of the lymphoid and hemopoietic systems, showed normal serum LAP activity. Fleisher, Butt and Huizegga[7] found "the greatest increase in enzymatic activity occurred in acute hepatitis." Smaller, but nevertheless significant increases also occurred in patients with infectious mononucleosis and portal cirrhosis, and levels became increasingly greater in obstructive jaundice, fatty liver, hepatic neoplasms, postnecrotic cirrhosis and chlorpromazine jaundice. On the basis of increased serum peptidase activity alone, a differentiation between these diseases therefore is not possible. In general, we are in agreement with these authors concerning the LAP activity in these conditions; however, "low-grade transient elevations" of the enzyme were not present in our series of patients with choledocholithiasis; on the contrary, elevations occurred in each case and were rather marked. We found relatively less serum LAP activity in patients with more stable hepatic diseases, such as diffuse hepatic fibrosis, than in those having a more active process such as viral hepatitis. It is of interest to note that a few patients with metastatic liver disease had normal levels of the enzyme.

To our knowledge, the only series of patients so far reported with carcinoma of the pancreas in which LAP activity was studied is that of Rutenburg, Goldbarg and Pineda[17]. Striking elevations were found in all of their 14 subjects with this condition. However, in our series of 19 patients, 4 showed normal levels of the enzyme. In the 15 remaining, values of LAP were comparable with those of patients with choledocholithiasis, acute pancreatitis or viral hepatitis. We are in agreement that "in jaundiced patients there was no correlation between leucine aminopeptidase activity and the intensity or duration of icterus." This statement would apply to patients with viral hepatitis as well.

The elevation of LAP found during pregnancy is presently obscure. Recent literature contains many reports concerning various enzymatic determinations during pregnancy. Serum lipase activity shows a progressive decrease during pregnancy, returning to normal 7 days after delivery (Mischel[14]). Newborn babies showed lipase values equal to that of the mother at the time of delivery. During the last trimester of pregnancy, a rise in serum alkaline phosphatase occurs (Jung and Stark[11], Young and Stark[23]) which drops rapidly during the first 24 hours following delivery and declines slowly during the next few days.

Conflicting reports concerning serum glutamic oxaloacetic transaminase activity during pregnancy have recently been reported. Quint and Spanos[15] showed that normal pregnancy and labor do not result in elevations of the enzyme. In fact, their mean for 64

determinations (12 units) was found to be lower than the usual mean for their laboratory (22 units). Pregnant patients with diabetes, degenerating fibroids, abruption of the placenta, intrauterine fetal death and mild preeclampsia had normal levels of GOT. They did several determinations on a nonpregnant patient with a twisted and infarcted dermoid cyst who showed no elevations of this enzyme. They noted 5 cord blood determinations were 5 to 10 units above that of the mother. Others reporting (Borglin[2], Glendening, Cohen and Page[8]) found normal values during normal pregnancy, but levels twice as high in cord blood. One investigator found a few elevations of GOT toward the end of pregnancy (Borglin[3]).

In a recent publication (Crisp, Miesfeld and Frajolia[6]) it was found that normal S–GOT values occurred during the course of pregnancy in 30 healthy subjects. The mean value for this group was near that found by Quint and Spanos[15], which was nearly half that expected for nonpregnant persons. In the communication of Crisp, Miesfeld and Frajolia[6], all but 5 of 23 patients with nontoxic complications of pregnancy demonstrated normal levels. Pregnant subjects with placental infarcts, essential hypertension and chronic renal disease had normal GOT activity. All 64 patients with preeclampsia and eclampsia had elevations of this enzyme. The severity of the disease was related to the level of the enzyme in the serum. Highest activities were well correlated with the 24-hour urinary albumin excretion. Other investigators (West and Zimmerman[22]) found both GOT and LDH (lactic dehydrogenase) to be normal in all stages of pregnancy. In fact, the GOT values were slightly lower than that of the average adult. During labor, however, a few patients had increased GOT levels and over one-half had normal LDH determinations. Cord blood showed elevated LDH results in 18 of 19 tested, and only 2 had marked S–GOT elevations (113 and 114 units). It has been suggested that the abnormal levels of the latter enzyme in patients with toxemia of pregnancy may be related to liver damage secondary to generalized vasospasm (Borglin[2], Crisp, Miesfeld and Frajolia[6]).

The relationship between the changes in the various enzymes described above and LAP activity in sera of patients with pregnancy or cancer is not clear. We have found that the greatest levels of this enzyme are present in the last trimester of pregnancy, and most especially at the time of delivery, rather than in patients with hepatobiliary-pancreatic disease. The significance of these high levels during the latter period of gestation is not understood. Since most levels of the enzyme in cord blood at the time of delivery were within normal limits, it is unlikely that the enzyme is released on the fetal side of the "placental barrier." Pancreatitis as a cause of that elevation is unlikely since Langmade and Edmondson[12], in their review, found only 53 cases of acute pancreatitis during pregnancy to which they added 9 of their own. None of the patients reported here had any clinical evidence of pancreatic or hepatic dysfunction.

Summary. A detailed account of an accurate and relatively simple, modified test for serum leucine aminopeptidate activity is given. A clinical unit of this enzyme is defined in terms of the amount of B-naphthylamine formed by enzymatic hydrolysis. The normal range is 50 to 150 clinical units. For accurate assay, nonhemolyzed serum should be used. It may be frozen until assay for periods of up to 6 weeks without loss of activity.

Serum leucine aminopeptidase activity was found to be elevated in most

patients with hepato-biliary-pancreatic disease. Carcinoma of the pancreas, choledocholithiasis, acute pancreatitis, viral hepatitis and metastatic liver disease produce comparable elevations in serum LAP activity. Therefore, in the individual case, the test will not distinguish these conditions. In a negative sense, however, a normal serum LAP value would be against the diagnosis of any one of these disorders, keeping in mind that a few cases will have normal levels.

The highest levels were not found in patients with carcinoma of the pancreas but, rather, in those patients in the last trimester of pregnancy and particularly at the time of delivery. However, the test would have little diagnostic value in pregnancy since no elevations are found in the first trimester. Since cord blood gave normal LAP levels in most instances, it appears that the enzyme may not cross the "placental barrier." A striking elevation is reported in a patient with a "missed" abortion. The transaminase determination in this patient was mildly increased. The possible causes of the high LAP activity in pregnancy are discussed. Its significance is obscure.

Within the limitations of all serum enzyme assays, the determination of serum LAP activity may be of value in the differential diagnosis of hepato-biliary-pancreatic diseases from other intraabdominal conditions. The test is not diagnostic of carcinoma of the pancreas in either jaundiced or nonjaundiced patients since occasional normal values were found in both conditions.

ACKNOWLEDGMENTS: We wish to express our appreciation to Mr. Chun Young Rhee for technical assistance. We are indebted to the Department of Obstetrics and Gynecology without whose cooperation an important part of the report would not have been possible. We would like to thank the Surgery Department for supplying us with patient material.

REFERENCES

1. **Adams, E., McFadden, M.,** and **Smith, E. L.:** J. Biol. Chem., **198**, 663, 1952.
2. **Borglin, N. E.:** J. Clin. Endocrinol. & Metab., **18**, 872, 1958.
3. Idem: Ibid., **18**, 878, 1958.
4. **Bratton, A. C.,** and **Marshall, E. J., Jr.:** J. Biol. Chem., **128**, 537, 1939.
5. **Burstone, M. S.:** J. Nat. Cancer Inst., **16**, 1149, 1956.
6. **Crisp, W. E., Miesfeld, R. R.,** and **Frajolia, W. J.:** Obst. & Gynec., **13**, 487, 1959.
7. **Fleisher, G. A., Butt, H. R.,** and **Huizegga, K. A.:** Proc. Staff Meet., Mayo Clinic, **32**, 410, 1957.
8. **Glendening, M. B., Cohen, A. M.,** and **Page, E. W.:** Proc. Soc. Exper. Biol. & Med., **90**, 25, 1955.
9. **Goldbarg, J. A.,** and **Rutenburg, A. M.:** Cancer, **11**, 283, 1958.
10. **Green, M. N., Tsou, K. C., Kressler, R.,** and **Seligman, A. M.:** Arch. Biochem. & Biophysics, **57**, 458, 1955.
11. **Jung, W.,** and **Stark, G.:** Arch. f. Kinderheilk., **154**, 23, 1956.
12. **Langmade, C. F.,** and **Edmondson, H. A.:** Surg. Gynec. & Obst., **92**, 43, 1951.
13. **Millonig, R. C.:** J. Bact., **72**, 301, 1956.
14. **Mischel, W.:** Ztschr. f. Geburtsh. und Gynäk., **144**, 62, 1955.
15. **Quint, B. C.,** and **Spanos, W. J.:** Unpublished data, personal communication, Dept. of Obstetrics and Gynecology, University of Kansas Med. Center, 1957.
16. **Reitman, S.,** and **Frankel, S.:** Am. J. Clin. Path., **28**, 1, 1957; **28**, 56, 1957.
17. **Rutenburg, A. M., Goldbarg, J. A.,** and **Pineda, E. P.:** New England J. Med., **259**, 469, 1958.
18. **Smith, E. L.:** *In* Sumner and Myrbäck's The Enzymes: New York, Academic Press, I (Part 2), 810, 1951.
19. Idem: Advances in Enzymology. New York: Interscience Publishers, Inc., **12**, 196, 1951

20. **Stern, K., Birmingham, M. K., Cullen, A.,** and **Richard, R.:** J. Clin. Invest., **30,** 84, 1951.
21. **Thomas, J. E.:** The External Secretions of the Pancreas. Springfield, Ill.: Charles C Thomas, 1950.
22. **West, M.,** and **Zimmerman, H. J.:** Am. J. Med. Sci., **235,** 443, 1958.
23. **Young, W.,** and **Stark, G.:** Zentralbl. f. Gynäk., **78,** 31, 1956.

SUMMARIO IN INTERLINGUA

Le Activitate Seral de Aminopeptidase de Leucina: Constatationes in Carcinoma del Pancreas, Pregnantia, e Altere Disordines

Es presentate un detaliate description de un accurate e relativemente simple modificate test pro activitate de aminopeptidase de leucina in le sero. Un unitate clinic de iste enzyma es definite con respecto al quantitate de B-naphthylamina formate per hydrolyse enzymatic. Le limites normal es 50 e 150 unitates. In le interesse del accuratia del resultatos, nonhemolysate seros deberea esser usate in le essayage. Le sero pote esser congelate ante le essayage durante periodos de usque a sex septimanas sin perdita de activitate.

Elevationes del activitate de aminopeptidase de leucina esseva constatate in le majoritate del patientes con morbo hepato-biliari-pancreatic. Carcinoma del pancreas, choledocholithiasis, pancreatitis acute, hepatitis virusal, e metastatic morbo hepatic produce comparabile elevationes del activitate seral de aminopeptidase de leucina. Assi le test non pote differentiar iste conditiones in le caso individual. Tamen, in terminos negative, le constatation de valores normal del activitate de aminopeptidase de leucina in le sero es un argumento contra le diagnose de ulle de iste disordines, ben que on debe memorar se que casos sporadic del morbos mentionate occurre con nivellos normal del enzyma.

Le plus alte nivellos non esseva trovate in patientes con carcinoma del pancreas sed plus tosto in patientes in le tertie trimestre de pregnantia e particularmente al tempore del parturition. Tamen, le test non esserea de grande valor diagnostic in casos de pregnantia proque nulle elevationes es trovate durante le prime trimestre. Viste que sanguine de cordon exhibiva normal nivellos de aminopeptidase de leucina in le majoritate del casos, il pare que le enzyma non transversa le "barriera placental." Un frappante elevation es reportate in un patiente con aborto retardate. Le determination de transaminase in iste caso monstrava valores levemente elevate. Le causas possibile del alte activitate de aminopeptidase de leucina in pregnantia es discutite. Su signification es obscur.

Intra le limitationes de omne essayage de enzymas seral, le determination del activitate de aminopeptidase de leucina in le sero pote esser de valor in le diagnose differential de morbos hepato-biliari-pancreatic vis-a-vis altere conditiones intraabdominal. Le test non es diagnostic pro carcinoma del pancreas in patientes icteric o nonicteric proque valores normal esseva incontrate in casos sporadic de ambe ille conditiones.

WHIRLPOOL-INDUCED PURPURA IN ANAPHYLACTOID PURPURA

By Captain Harold H. Hoefle, Jr., USAF (MC)

and

Captain Ralph C. Williams, Jr., USAF (MC)

(From the Department of Medicine, United States Air Force Hospital, Maxwell Air Force Base, Montgomery, Alabama)

The usual criteria of capillary fragility are often difficult to correlate with episodes of purpura in patients with the Henoch-Schönlein syndrome (Ackroyd[1], Peck, Rosenthal and Erf[5]), or anaphylactoid purpura. In the patient reported below, the tourniquet test (Rumpel-Leede) was repeatedly negative at a time when petechiae could be induced by immersion of the extremities in a whirlpool bath at 106° F. It suggested that response to whirlpool bath immersion may, in some instances, be a more sensitive indicator of capillary fragility than the various positive or negative pressure capillary fragility tests (Hess[3], Scarborough[7]).

Case Report. A 23-year-old white single male Air Force Staff Sergeant was admitted to the USAF Hospital, Wiesbaden, Germany, September 13, 1957, with complaints of pain and stiffness in the left hip after a fall. Two days before admission, the patient sustained an hyperflexion injury to the left hip while disembarking from an aircraft. Positive physical findings on admission were confined to limitation of motion of the left hip. Except for serial sedimentation rates ranging from 18 and 41 mm. per hour (Wintrobe), other laboratory studies, including serology, complete blood count, urinalysis, throat culture, antistreptolysin-o titer, C-reactive protein, total protein and A/G ratio, uric acid, blood urea nitrogen, roentgenograms of chest, left hip and knee, and electrocardiogram, were normal (Table 1).

Initial therapy included bed rest, aspirin, and physiotherapy. Two weeks after admission, he developed fever (100–100.6° F.) with pain, swelling, heat, and stiffness of the right wrist, right ankle, left knee, and left metatarsophalangeal joints. With continuation of aspirin and warm packs, his joint symptoms gradually abated; however, during the fourth week of hospitalization, showers of petechiae and purpuric spots were noted over the anterior surfaces of his legs between the knees and ankles. At this time repeated platelet counts, bleeding and clotting times, and Rumpel-Leede tourniquet tests were within normal limits. Because of petechiae and continued moderate arthralgia, he was transferred to the Maxwell Air Force Base Hospital for treatment, 5 weeks after the onset of his illness.

Physical examination at the Maxwell Air Force Base Hospital revealed slight swelling and increased heat over the left knee joint. Mild swelling of the right knee and ankle was noted but there were no joint effusions. A few petechiae were present over the pretibial areas bilaterally. Further laboratory studies included serial complete blood counts which were normal at weekly intervals; sedimentation rates varied between 33 and 48 mm. per hour (Wintrobe); platelet counts were 300,000 and 250,000 per c.mm.; and C-reactive proteins were trace to 1 plus on four determinations. Antistreptolysin-O titers were 50, 12, and 12 Todd units, lupus erythematosus preparations were negative, and direct Coombs' tests were likewise negative. Sternal bone marrow showed an M/E ratio of 4:1 with a normal percentage and maturation of megakaryocytes. Bleeding time, clotting time (Lee-White), and one-stage prothrombin time were normal. Tests for cryoglobulin, pyroglobulin, and Bence-Jones protein were negative. Serum electrophoretic pattern was normal. Serial urinalyses showed no evidence of microscopic hematuria (Table 1). The patient was continued on salicylate therapy, but whirlpool bath treatments were added because of continued complaints of pain in the joints of the lower extremities.

Shortly after immersing his legs in the whirlpool bath, the patient noted a recurrence of petechiae over his lower legs. More trials of whirlpool bath therapy were undertaken, and on repeated occasions petechiae were induced by immersion of either arms or legs in the whirlpool bath (106° F.). Concomitantly, prothrombin times, platelet counts bleeding and clotting times, and Rumpel-Leede tests were normal. A trial of hot, moist towel applications (at 106° F., with legs dependent) for 2-hour periods did not induce petechiae, while for the same interval of exposure, petechiae and purpuric spots could be produced by whirlpool bath immersion (Fig. 1). No hematuria was so induced.

It was felt that this patient had Henoch-Schönlein's, or anaphylactoid purpura associated with mild and recurrent arthralgia and a negative Rumpel-Leede tourniquet test. He was treated symptomatically with salicylates and graduated exercises. Slow return of joint function and subsidence of petechiae occurred over the next 6 weeks. The patient returned to duty without physical limitations or subsequent recurrence of symptoms over the next 5 months. Repetition of whirlpool immersion after recovery produced no petechiae.

TABLE 1

		Duration of Purpura			
	Sept. 13, 1957	*Sept. 28, 1957*	*Oct. 15, 1957*	*Nov. 16, 1957*	*Dec. 11, 1957*
White blood count	12,500	8,200	7,900	10,200	7,500
Hemoglobin (gm.%)	15.6	15.0	14.8	15.0	14.5
Sedimentation rate (Wintrobe)	18 mm./hr.	19 mm./hr.	35 mm./hr.	41 mm./hr.	33 mm./hr.
Urinalysis	neg.	neg.	neg.	neg.	neg.
Serology (VDRL)	neg.	—	neg.	—	—
Total protein and A/G ratio	6.8 with 4.5/2.3	—	—	—	8.2 with 6.1/2.1
C-reactive protein	trace	—	1 plus	—	1 plus
Serum electrophoresis	—	—	normal	—	normal
Blood urea nitrogen (mg./100 ml.)	—	—	—	12.5	15.0
Uric acid (mg./100 ml.)	2.7	—	—	—	4.0
Antistreptolysin-o titer (Todd units)	50	—	12	—	12
Platelet count	—	250,000	300,000	320,000	250,000
Bleeding time (Ivy)	—	2 min.	2 min.	1 min. 45 sec.	2 min. 15 sec.
Clotting time (Lee-White)	—	4 min.	3 min. 45 sec.	4 min. 20 sec.	3 min. 10 sec.
Prothrombin time (one-stage)	—	14 sec. 13 sec.C*	15 sec. 13 sec.C*	—	14 sec. 13 sec.C*
Latex fixation	—	—	—	neg.	—
LE preparation	—	—	neg.	—	neg.

*Control

Discussion. The cause of anaphylactoid purpura is not known. Indeed, since multiple sensitizing substances, as

well as previous streptococcal infections, have been suggested as factors in the pathogenesis of such purpura, it may be that the mechanisms for their production are numerous. That a defect in capillary endothelial wall may be operative has been advanced by Roskam[6]. Capillary microscopic studies by Humble[4] indicate that the petechial hemorrhages in anaphylactoid purpura occur only from the arteriolar portions of the capillary loop. Gairdner[2] suggests that the hemorrhagic manifestations of Henoch-Schönlein's purpura are secondary to a diffuse arteriolitis, but no consistent small arteriolar lesions have been noted by other investigators (Sturtevant and Graef[8]).

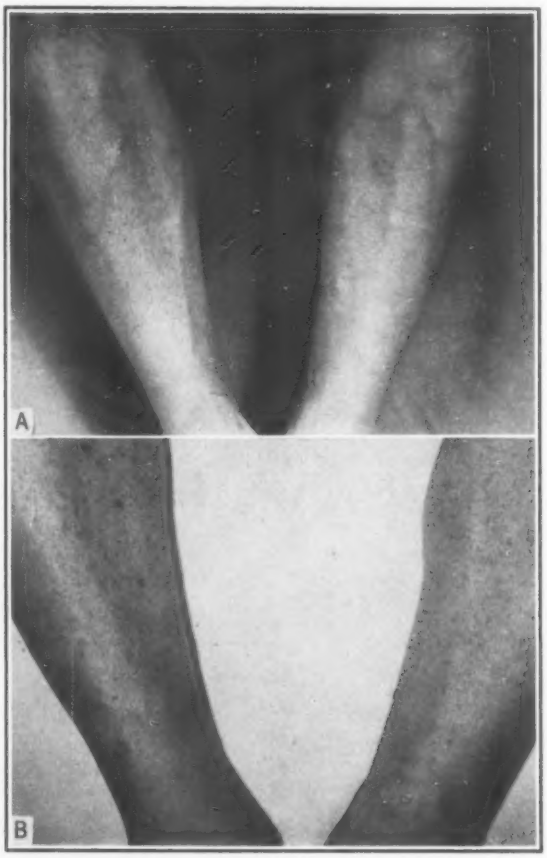


Fig. 1*a*.—Infra-red photograph of patient's legs before whirlpool immersion indicating no purpura and no vascular anomalies which could have been responsible for the petechiae.
Fig. 1*b*.—Patient's lower extremities after 15 minutes in the whirlpool bath at 106° F.

This case is reported in view of the interesting and reproducible episodes of purpura which were associated with immersion in whirlpool baths at a time when indices of blood coagulation and capillary fragility were normal. Though a negative tourniquet test was present, petechiae and larger areas of purpura

could be produced by the whirlpool, but not by constant hot packs at the same temperature (106° F.) maintained over a like period of time. It is suggested that extremity immersion in the whirlpool produced local vascular trauma rather than a generalized systemic reaction, by the failure to induce hematuria. The possibility exists that the salicylates which the patient received may have been a factor in the induction of his purpura. This is unlikely, since continued salicylate administration was accompanied by a gradual fading of the purpuric manifestations. Moreover, challenging with salicylates 3 months after the illness had subsided, failed to elicit either spontaneous petechiae or abnormal skin phenomena on whirlpool bath immersion. Since the tourniquet test and the snake venom test may be positive or negative in Schönlein's purpura (Peck, Rosenthal and Erf[5]), testing with whirlpool bath immersion may be helpful in assessing capillary fragility. It is postulated that the combination of heat and mechanical trauma was sufficient to induce purpura in the capillary beds exposed to the whirlpool. Such effects are not present in normal subjects undergoing whirlpool bath immersion, and could not be demonstrated in this patient after recovery from his acute illness.

Summary. A case of anaphylactoid purpura presenting unusual diagnostic features is reported.

This patient developed joint manifestations (tenderness, swelling and heat), petechiae, and purpura. The usual signs of capillary fragility were repeatedly negative, while whirlpool bath immersion (106° F.) easily induced petechiae.

These findings suggest that whirlpool bath immersion may be of value in assessing capillary fragility when other tests of capillary integrity are normal.

REFERENCES

1. **Ackroyd, J. F.:** Am. J. Med., **14**, 605, 1953.
2. **Gairdner, D.:** Quart. J. Med., **17**, 95, 1948.
3. **Hess, A. F.:** Arch. Int. Med., **17**, 203, 1916.
4. **Humble, J. G.:** Blood, **4**, 69, 1949.
5. **Peck, S. M., Rosenthal, N.,** and **Erf, L.:** Arch. Dermat. & Syph., **35**, 831, 1937.
6. **Roskam, J.:** Biol. et Path., **27**, 856. 1956.
7. **Scarborough, H.:** Edinburgh Med. J., **48**, 555, 1941.
8. **Sturtevant, M.,** and **Graef, I.:** Med. Clin. N. America, **17**, 91, 1933.

SUMMARIO IN INTERLINGUA

Petechias, Inducite per un Banio de Aqua Calide in Vortice, in un Caso de Purpura Anaphylactoide

Es reportate un caso de purpura anaphylactoide con inusual aspectos diagnostic.

Le patiente disveloppava manifestationes articular (sensibilitate, tumescentia, calor), petechias, e purpura. Le signos usual de fragilitate capillar esseva repetitemente negative, durante que petechias esseva facilemente inducite per le immersion del extremitates in aqua calide in vortice a un temperatura de 106 F.

Iste constatationes pare indicar que le immersion in un banio in vortice es possibilemente de valor in estimar le fragilitate capillar quando altere tests del integritate capillar resulta in reactiones normal.

HYPERCALCIURIA IN HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE)*

By Robert B. Litin, M.D.†
FELLOW IN UROLOGY, MAYO FOUNDATION

Raymond V. Randall, M.D.
SECTION OF MEDICINE

Norman P. Goldstein, M.D.
SECTION OF NEUROLOGY

Marschelle H. Power, Ph.D.
SECTION OF BIOCHEMISTRY

AND

Grant R. Diessner, M.D.
SECTION OF MEDICINE

(From the Mayo Clinic and Mayo Foundation,‡ Rochester, Minnesota)

It has been demonstrated repeatedly that there is a disturbance in the metabolism of copper and amino acids in hepatolenticular degeneration (Wilson's disease). Bush and associates[3] have summarized the abnormalities in the metabolism of copper as follows: a decreased plasma concentration of total copper and of ceruloplasmin, an alpha-globulin copper compound; an increased concentration of copper in the tissues, especially in the liver and brain; and an increased excretion of copper in the urine. In 1948 Uzman and Denny-Brown[25] demonstrated an increased excretion of amino acids in the urine in hepatolenticular degeneration which, with few exceptions (Bearn and Kunkel[1], Stein, Bearn and Moore[22]), appears to be a feature of the disease. The amino-aciduria is not associated with an increase in the concentration of amino acids in the plasma (Uzman and Hood[26]) and is thought to be due to a failure of tubular reabsorption of amino acids filtered through the glomeruli (Cartwright *et al.*[4], Uzman[24], Uzman *et al.*[27]).

The findings of glycosuria (Bearn and Kunkel[1]) and uricosuria (Mahoney *et al.*[17]) in some patients with hepatolenticular degeneration suggest actual impairment of renal function. Hodges, Kirkendall and Gubler[11] studied 4 patients having hepatolenticular degeneration and found a consistent pattern of reduced renal flow of plasma and lowered rate of glomerular filtration. Bearn, Yü and Gutman[2] confirmed the presence of reduced renal flow of plasma and decreased glomerular-filtration rate in patients with hepatolenticular degeneration and found that the degree of impairment roughly parallels

*Read in part at the meeting of the American Academy of Neurology, Los Angeles, California, April 13 to 18, 1959.

†Requests for reprints should be addressed to Dr. Raymond V. Randall, Mayo Clinic, Rochester, Minnesota.

‡The Mayo Foundation, Rochester Minnesota, is a part of the Graduate School of the University of Minnesota.

the severity of duration of overt disease. They also noted that tubular secretory capacity was reduced, especially if the disease was advanced, and that in 4 of their patients the maximal capacity of the tubules to reabsorb glucose was reduced.

The finding of hypercalciuria in a patient with hepatolenticular degeneration (case 1) made us wonder whether this was further evidence of intrinsic renal dysfunction and prompted us to study the urinary excretion of calcium in 4 additional patients with hepatolenticular degeneration.

Report of Cases. Five consecutive patients seen at the Mayo Clinic with hepatolenticular degeneration were selected for study. None of the patients had received treatment for this condition for 1 to 4 months prior to the study. In each case the diagnosis was made by the findings of neurologic manifestations consistent with the disease, typical Kayser-Fleischer rings and increased urinary excretion of copper and alpha-amino nitrogen. In no case was a family history of hepatolenticular degeneration obtained.

Table 1 summarizes the pertinent biochemical findings in our 5 cases.

Case Reports. CASE 1.—A 40-year-old white man registered at the clinic in November, 1955, with a 2-year history of slurred speech and tremor of both hands. The history included the passage of a stone from the left kidney in 1947 and pelviolithotomy of the left kidney in 1950 for a recurrent stone.

Physical examination revealed the liver to be palpable two fingerbreadths below the right costal margin while the spleen was barely palpable. On neurologic examination, the patient was found to have minimal tremor of the hands at rest, mild static tremor of the head and upper extremities with considerable tremor of the upper extremities on movement. The movement tremor, as well as the static tremor, of the upper extremities had a wing-flapping characteristic. Typical Kayser-Fleischer rings were present.

Results of tests for hepatic function were normal. Glycosuria was noted; the value for fasting blood sugar was normal, but results of the glucose tolerance test were abnormal (mg. per 100 ml. of blood: fasting, 109; 1 hour, 195; 2 hours, 176 and 3 hours, 100). The renal stone which the patient had passed in 1947 was analyzed in our laboratory and found to contain calcium carbonate and calcium phosphate. An excretory urogram showed bilateral nephrocalcinosis. Roentgenograms of the skeleton showed an old fracture of the right sixth rib, slight intra-articular calcification of the right wrist, an old fracture of the distal end of the right radius and hypertrophic changes of the lumbar portion of the spinal column.

CASE 2.—A 32-year-old white man registered at the clinic in June, 1957. He stated that his illness began in 1950 with a movement tremor of the right upper extremity followed by tremor of the left arm the next year. In 1954 he noted difficulty in walking, and in 1956 dysarthria developed.

General examination did not show evidence of abnormality. Neither the spleen nor the liver was palpable. Neurologic examination revealed Kayser-Fleischer rings and an advanced wing-flapping tremor on movement of the upper extremities. There was also a marked terminal intention tremor on the finger-nose test. The patient was ataxic and had tremor of both lower extremities when walking. Dysarthria, manifested by a disturbance of articulation, also was present.

The results of laboratory tests of hepatic function were normal. An excretory urogram was done because of the presence of microscopic hematuria; it showed a 4 mm. stone in the lower calyx of the left kidney. Roentgenograms of the skeleton showed degenerative changes of the right shoulder, elbow, knee and wrist, with an old fracture of the right ulnar styloid process.

CASE 3.—An 11-year-old boy was first seen at the clinic in 1946 when a diagnosis of convulsive disorder was made and phenobarbital was prescribed.

He returned in 1952 because of cramps in his extremities. Kayser-Fleischer rings and hepatosplenomegaly were noted and a diagnosis of hepatolenticular degeneration was made; the results of neurologic examination were normal. Needle biopsy of the liver showed the presence of cirrhosis associated with a rather definite inflammatory component. He received intermittent treatment with BAL.

Subsequent examinations in 1953 and 1954 revealed that the hepatolenticular degeneration had not progressed. However, early in 1957, slowness of movement, slurred speech, tremor of the arms at rest, drooling of saliva and swelling of the lower extremities developed and he gained 20 pounds.

Physical examination in September, 1957,

TABLE 1.—HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE): BLOOD AND URINARY FINDINGS IN 5 PATIENTS

	Blood															*Urine*		
	Serum									*Plasma*								
Case	Calcium (mg. per 100 ml.)	Phosphate (mg. per 100 ml.)	Alkaline phosphatase (King-Armstrong units per 100 ml.)	Serum uric acid (mg. per 100 ml.)	Serum protein albumin/globulin (gm. per 100 ml.)	Serum bilirubin direct/indirect (mg. per 100 ml.)	Thymol turbidity (units)	Cholesterol-cephalin flocculation	Copper oxidase test 0 = no enzymatic activity	Urea (mg. per 100 ml.)	Sodium (mEq. per L.)	Potassium (mEq. per L.)	Chlorides (mEq. per L.)	Carbon dioxide (mEq. per L.)	Fasting blood sugar (mg. per 100 ml.)	Bromsulphalein dye retention (%)	Copper* (mg. per 24 hr.)	Glucose	Alpha amino nitrogen* (mg. per 24 hr.)
1	9.7	1.8	11.8	1.8	6.12 4.10 2.02	0/0.6	1	0	0	40	136	3.3	109	15	98	0	1.04	+	924
2	9.6	2.9	7.4	2.3	6.45 4.50 1.95	0/0.74	2	2 +	0	36	136	4.1	105	22	97	0	1.00	+	570
3	9.2	3.8	12.9	1.4	5.30 3.50 1.80	0/2.24	4	3 +	0	16	131	4.2	108	22	95	16	0.57	0	509
4	9.6	3.3	5.3	2.0	6.60 4.45 2.15	0/0.49	2	2 +	0	30	129	4.4	106	24	98	0	0.28	0	458
5	9.4	2.6	4.0	1.4	—	0/1.52	—	—	—	24	137	3.8	107	24	99	0	0.42	0	669

*Each value is the mean of three 24-hour periods.

showed advanced hepatosplenomegaly, fetor hepaticus and edema of the legs. Neurologic examination disclosed masking of the facies, a decrease in the alternate motion rate of the tongue and extremities, monotonous voice, increased tone of the neck muscles, a static tremor of the upper extremities and a Babinski sign on the right side.

Tests for hepatic function showed abnormalities, as noted in Table 1. An excretory urogram was normal. Leukopenia had been noted repeatedly since 1952 (1300 to 2700 leukocytes per c.mm.) Further tests disclosed relative lymphocytosis and decreased number of platelets (24,000 to 53,000 per c.mm.). A roentgenographic survey of the skeleton did not disclose any abnormality.

CASE 4.—A 21-year-old white woman was seen in February, 1958, with a history of "nervousness" and tremor of the right hand present for 4 years. She had also noted incoordination of this hand when sewing or knitting.

Results of general examination were normal. The liver and spleen were not palpable. Neurologic examination revealed the presence of Kayser-Fleischer rings, minimal ataxia on tandem walking, and a static tremor of the right upper extremity with a wing-flapping movement of the right wrist. The muscle stretch reflexes were more active in the right extremities than in the left and the Babinski sign was present on the right.

Tests of hepatic function gave normal results. An excretory urogram was also normal. Roentgenograms of the skeleton did not show abnormalities.

CASE 5.—A 26-year-old white woman registered at the clinic in June, 1958. A diagnosis of hepatolenticular degeneration had been made in 1948, at which time the patient had noted the onset of intention tremor of the right hand and slow, stammering speech. In the next few years, the tremor involved all 4 extremities, and the patient had become so ataxic that she had been bedfast since 1953. Her speech had deteriorated to the point where it was barely intelligible.

General physical examination showed normal results; neither the liver nor the spleen was palpable. Neurologic examination revealed the presence of Kayser-Fleischer rings, marked tremor of all extremities on movement, a marked terminal intention tremor and almost total decomposition of movement of all extremities. There were rigidity on passive motion of all 4 extremities and severe cerebellar ataxia. The speech was extremely dysarthric.

Despite the severe neurologic deficit, the tests of hepatic function gave normal results, but leukopenia (2100 and 3900 per c.mm.) and thrombocytopenia (76,000 per c.mm.) were present.

Method. The urinary excretion of calcium was measured in each patient over a 3-day period during which time the patient was given a diet containing a known amount of calcium.

DIET. The diet was begun at the evening meal prior to the 3-day period of observation and contained 2223 calories made up of 62 gm. of protein, 111 gm. of fat and 244 gm. of carbohydrate per 24 hours. Distilled water as desired was used as drinking water. An estimation of the daily intake of calcium and copper was made by analyzing an aliquot of a mixture of a 24-hour diet plus 1900 ml. of distilled water. By this method the daily intake of calcium and of copper was estimated to be 213 mg. and 2.93 mg. respectively. Food not eaten was not analyzed or subtracted from the total amount. However, each patient was instructed to eat everything and in no case was a significant amount of food left uneaten.

COLLECTION OF URINE. Chemical determinations were done on three successive specimens of urine collected over 24-hour periods while the patients were eating the previously described diet. The urine was collected in acid-washed bottles and analysis was started the day each collection was completed.

CHEMICAL METHODS. Venous blood for determination of plasma electrolytes was drawn under oil into a tube containing purified heparin. The sodium and potassium were estimated in the flame photometer; the carbon dioxide content of the plasma was measured by the method of Van Slyke and Neill[20] and chlorides were measured by a modification of the method of Keys[12]. Values for other constituents of the blood were determined as follows: urea, by a modification of the urease method of Van Slyke and Cullen[28]; glucose, by the method of Folin and Wu[8]; inorganic phosphate, by a modified method of Gomori[9], and calcium, by permanganate titration of oxalate as precipitated from serum. The alkaline phosphatase in the serum was estimated by the method of King and Armstrong[13] and the serum uric acid by the method of Folin[7]. Other values were determined as follows: serum bilirubin, by the method of Powell[18]; serum proteins, by a modification of the biuret procedure (Kingsley[14]); prothrombin time, by the modified Quick method[19]; and the bromsulphalein

(Rosenthal and White[21]), cephalin cholesterol flocculation (Hanger[10]) and the thymol turbidity (MacLagan[16]), by standard methods. Copper oxidase activity was determined by the method of Ravin[20].

Calcium in the urine was precipitated as the oxalate and determined acidimetrically after conversion of the oxalate to carbonate. For determination of copper in the urine, aliquots were ashed with a mixture of nitric and perchloric acids, after which copper was reacted with zinc dibenzyldithiocarbamate according to the procedure of Stone, Ettinger and Gantz[23].

Results and Comment. Table 2 shows the urinary excretion of calcium in our 5 patients. With the diet used in this study, a value for urinary calcium in excess of 170 mg. per 24 hours can usually be considered to be above normal (Litin[15]). By this criterion, 4 of our 5 patients had hypercalciuria. It is of interest that the only patient who had a normal excretion of calcium in the urine (case 4) had the shortest duration and mildest form of hepatolenticular degeneration as judged by the neurologic manifestations. One patient (case 1) had nephrocalcinosis and a history of nephrolithiasis, and another patient (case 2) had a stone in the left kidney. Excretory urograms in 2 of the other patients were normal (Table 2).

It is not known whether hypercalciuria in our patients was caused primarily by increased absorption of calcium from the gastrointestinal tract, a renal defect, or skeletal disease. The hypercalciuria was not associated with hypercalcemia or an elevated amount of alkaline phosphatase in the serum. The first patient (case 1) was unique among our patients in that the values for plasma electrolytes suggested renal tubular acidosis (Table 1). The chlorides averaged 109 mEq. per liter, the carbon dioxide combining power averaged 15 mEq. per liter and the potassium averaged 3.3 mEq. per liter of plasma. The urine had a pH of 6.6, a titratable acidity of 12.6 mEq. in 24 hours, and the value for ammonia was 25.6 mEq. in 24 hours. However, the oral administration of 20 gm. of sodium bicarbonate per day for 5 days did not produce significant change in the plasma chlorides and carbon dioxide combining power, or the urinary excretion of calcium. This observation is inconsistent with a diagnosis of the type of renal tubular acidosis associated with hypercalciuria, which is known as the Lightwood-Butler-Albright syndrome.

TABLE 2.—HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE): URINARY EXCRETION OF CALCIUM AND ROENTGENOGRAPHIC FINDINGS IN 5 PATIENTS

Case	*Calcium mg. per 24 Hours*	*Roentgenographic Evidence in Kidneys*
1	192 207 200 Ave. 200	Bilateral nephrocalcinosis
2	233 239 246 Ave. 239	Stone, in left kidney
3	350 404 332 Ave. 362	Normal
4	126 116 125 Ave. 122	Normal
5	362 210 292 Ave. 288	No roentgenograms made

A review of the literature revealed that the only study presenting data on the urinary excretion of calcium in hepatolenticular degeneration is that of Cooper and associates[5]. They reported what they considered to be a derangement of calcium metabolism in

one of 6 patients having this condition. The patient in question was a 13-year-old boy who had been studied previously over a period of several years by other investigators who had found his level of calcium to average 8.3 mg.; phosphorus 2.8 mg.; and alkaline phosphatase, 14.7 Bodansky units, each per 100 ml. of serum. Roentgenograms of the knees and wrists obtained 3 years before the patient was first seen by Cooper and his associates had not revealed abnormalities, but roentgenograms obtained 1½ years later showed evidence of a moderate degree of decalcification of all the long bones. At the time that Cooper and his colleagues studied this patient the calcium measured 11.3 mg., the phosphorus 4.0 mg., and the alkaline phosphatase 5.4 Bodansky units, each per 100 ml. of serum. While the patient was receiving a diet consisting primarily of milk, the urine for a representative day contained 650 mg. of calcium.

For a number of years it has been known that hepatolenticular degeneration may be associated with skeletal abnormalities such as demineralization, spontaneous fractures, pseudofractures and osteoarthritis. In a recent review of the roentgenographic aspects of this problem, Finby and Bearn[6] postulated that the skeletal changes may be related to a disturbance of phosphate metabolism and also that the abnormal metabolism of copper may play a role in these changes. It is interesting to speculate whether hypercalciuria may be associated with some of the skeletal abnormalities in hepatolenticular degeneration.

Recently, Ying-K'un[30] reported roentgenographic findings of skeletal demineralization in 4 of 10 patients with hepatolenticular degeneration. Two of the 4 patients were said to show a negative calcium balance, as did one other patient who did not have roentgenographic evidence of skeletal demineralization. However, no data on urinary calcium were included in this report.

Additional study is needed to determine the frequency and cause of hypercalciuria in hepatolenticular degeneration. It also will be interesting to learn whether renal stones or nephrocalcinosis is common in such patients, and whether there is a relationship between hypercalciuria and the skeletal defects associated with this disease. Since abnormalities in renal function have been demonstrated in hepatolenticular degeneration, the hypercalciuria which we have observed may well be the result of a renal tubular defect. Support for, or denial of, such a hypothesis must await further investigation.

Summary. Hypercalciuria was noted in 4 of 5 patients with hepatolenticular degeneration. One patient was found to have bilateral nephrocalcinosis, and another had a stone in the left kidney. The cause of hypercalciuria is not known, but it may represent still another renal tubular defect in hepatolenticular degeneration.

REFERENCES

1. **Bearn, A. G.,** and **Kunkel, H. G.:** J. Lab. & Clin. Med., **45,** 623, 1955.
2. **Bearn, A. G., Yü, T. F.,** and **Gutman, A. B.:** J. Clin. Invest., **36,** 1107, 1957.
3. **Bush, J. A., Mahoney, J. P., Markowitz, H., Gubler, C. J., Cartwright, G. E.,** and **Wintrobe, M.M.:** Ibid., **34,** 1766, 1955.
4. **Cartwright, G. E., Hodges, R. E., Gubler, C. J., Mahoney, J. P., Daum, K., Wintrobe, M. M.,** and **Bean, W. B.:** Ibid., **33,** 1487, 1954.
5. **Cooper, A. M., Eckhardt, R. D., Faloon, W. W.,** and **Davidson, C. S.:** Ibid., **29,** 265, 1950.
6. **Finby, N.,** and **Bearn, A. G.:** Am. J. Roentgenol., **79,** 603, 1958.

7. **Folin, O.:** J. Biol. Chem., **54**, 153, 1922.
8. **Folin, O.,** and **Wu, H.:** Ibid., **41**, 367, 1920.
9. **Gomori, G.:** Inorganic Phosphate. *In* Reiner, M.: Standard Methods of Clinical Chemistry. New York: Academic Press, Inc., vol. 1, pp. 84–87, 1953.
10. **Hanger, F. M.:** Tr. Assn. Am. Phys., **53**, 148, 1938.
11. **Hodges, R. E., Kirkendall, W. M.,** and **Gubler, C. J.:** J. Lab. & Clin. Med., **47**, 337, 1956.
12. **Keys, A.:** J. Biol. Chem., **119**, 389, 1937.
13. **King, E. J.,** and **Armstrong, A. R.:** Canad. Med. Assn. J., **31**, 376, 1934.
14. **Kingsley, G. R.:** J. Lab. & Clin. Med., **27**, 840, 1942.
15. **Litin, R. B.:** Unpublished data.
16. **MacLagan, N. F.:** Brit. J. Exper. Path., **25**, 234, 1944.
17. **Mahoney, J. P., Sandberg, A. A., Gubler, C. J., Cartwright, G. E.,** and **Wintrobe, M. M.:** Proc. Soc. Exper. Biol. & Med., **88**, 427, 1955.
18. **Powell, W. N.:** Am. J. Clin. Path., **14**, 55, 1944.
19. **Quick, A. J., Stanley-Brown, M.,** and **Bancroft, F. W.:** Am. J. Med. Sci., **190**, 501, 1935.
20. **Ravin, H. A.:** Lancet, **1**, 726, 1956.
21. **Rosenthal, S. M.,** and **White, E. C.:** J. Am. Med. Assn., **84**, 1112, 1925.
22. **Stein, W. H., Bearn, A. G.,** and **Moore, S.:** J. Clin. Invest., **33**, 410, 1954.
23. **Stone, I., Ettinger, R.,** and **Gantz, C.:** Anal. Chem., **25**, 893, 1953.
24. **Uzman, L. L.:** Am. J. Med. Sci., **226**, 645, 1953.
25. **Uzman, L.,** and **Denny-Brown, D.:** Ibid., **215**, 599, 1948.
26. **Uzman, L. L.,** and **Hood, B.:** Ibid., **223**, 392, 1952.
27. **Uzman, L. L., Iber, F. L., Chalmers, T. C.,** and **Knowlton, M.:** Ibid., **231**, 511, 1956.
28. **Van Slyke, D. D.,** and **Cullen, G. E.:** J. Biol. Chem., **19**, 211, 1914.
29. **Van Slyke, D. D.,** and **Neill, J. M.:** Quoted by **Peters, J. P.,** and **Van Slyke, D. D.:** Quntitative Clinical Chemistry. Baltimore: The Williams & Wilkins Company, **2**, 283–289, 1932.
30. **Ying-K'un, F.:** Chinese Med. J., **75**, 631, 1957.

SUMMARIO IN INTERLINGUA

Hypercalciuria in Degeneration Hepatolenticular (Morbo de Wilson)

Hypercalciuria esseva notate in 4 inter 5 patientes con degeneration hepatolenticular. Esseva trovate que un del patientes habeva nephrocalcinosis bilateral. Un altere habeva un calculo in le ren sinistre. Le causa de hypercalciuria non es cognoscite, sed il es possibile que il se tracta de ancora un defecto reno-tubular in degeneration hepatolenticular.

SUMMARIO IN INTERLINGUA

(See page 584 for original article)

Conformation Corporee, Estrogenos Urinari, Cholesterol del Sero, e Morbo de Arteria Coronari in Adulte Masculos de Racia Blanc

In masculos comparabile in etate, racia, origine ethnic, activitate physic, e parametros cultural e dietari, le modo de estrogenuria per 24 horas esseva simile in le varie somatotypos. Similemente, nulle significative differentia esseva trovate con respecto al modo del excretion de estrogeno per 24 horas inter masculos "normal" e masculos con signos clinic de atherosclerosis coronari.

PROGRESS
OF
MEDICAL SCIENCE

RADIOLOGY

UNDER THE CHARGE OF

DAVID M. GOULD, M.D.
PROFESSOR OF RADIOLOGY, UNIVERSITY OF COLORADO MEDICAL CENTER
DENVER, COLORADO

AND

JOHN G. MCAFEE, M.D.
ASSOCIATE PROFESSOR OF RADIOLOGY, THE JOHNS HOPKINS UNIVERSITY AND HOSPITAL
BALTIMORE, MARYLAND

A RADIOLOGICAL ANALYSIS OF DISSEMINATED LUNG DISEASE

BY DAVID M. GOULD, M.D.*

AND

GLENN V. DALRYMPLE, M.D.†

WHEN a chest roentgenogram reveals bilateral, widespread lung disease, the physician may succumb to a defeatist attitude toward diagnosis because of a profusion of known causes. This attitude is neither productive nor warranted. A thoughtful analysis of the Roentgen pattern and the correlation of the clinical findings can eliminate a large number of possible etiologies and thereby narrow the field to a few of the most likely causes[91].

Several diseases produce such distinctive patterns that they may be considered pathognomonic of these disease entities. The calcific "'snow-storm" of pulmonary alveolar microlithiasis, the crescent calcifications of porocephalosis, the healed miliary calcifications of histoplasmosis, and the contracted butterfly pattern of the third stage of silicosis are examples of distinctive patterns produced by specific etiologies.

The radiologist who claims a high degree of diagnostic accuracy from the objective interpretation of chest films may be deluding himself. Between the extreme of over-confidence and defeatism, lies a moderate and useful attitude.

Authors, who write general articles concerning disseminated lung disease, emphasize a similarity of patterns, while those who write about a specific etiology emphasize a distinctive character. An appreciable percentage of cases will not yield to clinical and radiological analysis and must be ultimately diagnosed by a study of tissues

*Professor and Head, Department of Radiology, formerly of University of Arkansas Medical Center, Little Rock, Arkansas, now of University of Colorado Medical Center, Denver, Colorado.
†Resident in Radiology, University of Arkansas Medical Center, Little Rock, Arkansas.

taken before or after death. A small percentage of cases even after necropsy cannot be assigned to a known etiological category.

In the older literature, the scattered, seeded, bilateral, and widespread pattern of miliary tuberculosis was considered the prototype of disseminated lung disease. Diffuse pulmonary diseases which bore a resemblance to miliary tuberculosis were catalogued. In 1938, King[61] listed 10 causes: miliary tuberculosis, sarcoid, fungus, periarteritis nodosa, miliary carcinomatosis, silicosis, bronchopneumonia, psittacosis, bronchiolectasis, and unknown. In

TABLE 1.—ETIOLOGY OF DISSEMINATED LUNG DISEASE

(in alphabetical order)

A

1. Acetylene
2. Actinomycosis
3. Alveolar cell carcinoma[113]
4. Amebiasis[119]
5. Amniotic fluid
6. Amyloidosis[118]
7. Anemias, sickle, Cooley's
8. Anomalous venous return
9. Anthracosis (coal)[89]
10. Artefacts
11. Arteriovenous fistulae[112]
12. Asbestosis (silicates)
13. Ascariasis
14. Aspergillosis
15. Atelectasis[117]
16. Atypical pneumonia

B

17. Bagassosis (bagasse)
18. Baritosis (baryta)
19. Barium[26]
20. Beryllosis (beryllium)[93]
21. Blastomycosis[50]
22. Blebs, Bullae[11]
23. Bronchiectasis[31]
24. Bronchiolar Carcinoma
25. Bronchiolectasis
26. Bronchiolitis
27. Bronchiolitis obliterans
28. Bronchitis, chronic
29. Bronchogenic carcinoma
30. Bronchopneumonia
31. Byssinosis (cotton lint)

C

32. Carbon tetrachloride
33. Carcinoma (metastatic)
34. Coccidioidomycosis[7,81]
35. Concussion, blast[42]
36. Congenital cystic disease[73]
37. Congenital heart, left to right shunt

C—(Continued)

38. Cryptococcosis[57,122]
39. Cysticercosis
40. Cystic fibrosis (mucoviscidosis)[62]
41. Cytomegalic inclusion disease[30]

D

42. Drowning
43. Dysautonomia (Riley-Day syndrome)[65,77]

E

44. Echinococcosis
45. Edema, pulmonary[19,39]
46. Emphysema[24]
47. Eosinophilia, tropical
48. Eosinophilic granuloma
49. Erythema nodosum[6,25]
50. Esophageal disease (aspiration)
51. Expiration film

F

52. Farmer's lung[18,34]
53. Fat emboli
54. Fibrocystic disease[55]
55. Fibrosis[72,92,102]
56. Filariasis
57. Foreign bodies
58. Fractures, ribs
59. Friedlander's pneumonia[78]
60. Fuso-spirochetal infection

G

61. Gasoline
62. Gaucher's disease[79]
63. Geotrichosis[120]
64. Graphite (carbon)

H

65. Hand-Schüller-Christian disease[90]
66. Hemorrhage

TABLE 1.—*(Continued)*

67. Hemosiderosis (mitral)[23]
68. Histocytosis X[84,121]
69. Histoplasmosis[35,59,85]
70. Hodgkin' disease[12]
71. Hyaline membrane disease[13]

I

72. Idiopathic pulmonary hemosiderosis[9,32]
73. Infection
74. Infectious mononucleosis[1]
75. Interstitial fibrosis (Hamman-Rich syndrome)[45,97,116]

K & L

76. Kerosene[33]
77. Leptospirosis[106]
78. Letterer-Siwe's Disease
79. Leukemia
80. Lighter fluid
81. Lipiodol
82. Lipoid aspiration pneumonia[46,54,100]
83. Loeffler's pneumonitis[51,110]
84. Lymphoma

M

85. Melioidosis, glanders[80]
86. Metallic particles
87. Microlithiasis, pulmonary[108]
88. Mitral disease
89. Moniliasis
90. Multiple aseptic emboli
91. Multiple myeloma, ribs
92. Mustard gas

N

93. Neoplasm[98]
94. Neurofibromatosis
95. Neurologic defect (aspiration)
96. Nitrogen dioxide, NO_2
97. Nocardiosis[44]

O

98. Ornithosis[93]
99. Osteoblastic metastasis, ribs
100. Osteochondromas, ribs
101. Osteopoikilosis, ribs

P

102. Paragonimiasis[75,114]
103. Passive congestion
104. Pertussis
105. Phosgene

P—(Continued)

106. Plague
107. Pneumatoceles, vanishing lung disease
108. Pneumococcus
109. Pneumoconiosis[49,71]
110. Pneumocystis carinii[2]
111. Polyarteritis nodosa[20,63,94,107]
112. Polycythemia vera
113. Porocephalosis[111]
114. Porotic folded fractures, ribs
115. Pregnancy
116. Proteinosis, pulmonary alveolar[96]
117. Psittacosis
118. Pulmonary adenomatosis

Q & R

119. Q fever[82]
120. Reticulum cell sarcoma
121. Rheumatic pneumonitis
122. Rachitic rosary, ribs
123. Rocky Mt. spotted fever
124. Rubeola, measles[16]

S

125. Salmonella[43]
126. Sarcoidosis[15,36]
127. Sarcoma (metastatic)
128. Schistosomiasis
129. Scleroderma[74,83,123]
130. Scorbutic bayonet, ribs
131. Siderosis (iron)[99]
132. Silicosis (silica)[14,58,86,87]
133. Silo-filler's disease[70]
134. Sporotrichosis[88]
135. Stannosis (tin)[21]
136. Staphylococcus[52,103]
137. Steam, hot air
138. Streptococcus
139. Sulfur dioxide, SO_2
140. Systemic lupus erythematosus

T

141. Tobaccosis (tobacco)
142. Toxoplasmosis
143. Tuberculosis[22,48]
144. Tuberous sclerosis
145. Tularemia[17]
146. Turpentine

U–V–W

147. Unknown, undiagnosed
148. Varicella, chickenpox[66,109]
149. Visceral Larva migrans[60]
150. Wegener's granulomatosis[53,64]

1942, Austrian and Brown[3] added 12 more categories to total 22: pyemia, atelectasis, congenital cystic disease, sarcomatosis, lipoid pneumonia, xanthomatosis, chronic passive congestion, polycythemia vera, brucellosis, Hodgkin's disease, leukemia, and lupus erythematosus disseminata. In 1948, Felson and Heublein[29] collected 53 more causes for a total of 75. They arranged the etiologies in a rational medical classification. From a perusal of the literature and from personal experience, 150 etiologies which produce a pattern of disseminated lung disease have been gathered and arranged in alphabetical order (Table 1).

In order to bridge the gap between the chest film with disseminated lesions and the multitude of causes, the attending physician and the radiologist can help each other immensely by pooling information, stimulating particular lines of inquiry, and by the final critical analysis of all the available data.

The attending physician contributes historical information of great importance such as: age, race, sex, occupational history, birthplace, home, travels, economic status, family history, allergies, past history, medication, and treatment. Details concerning pain, sputum, hemoptysis, and dyspnea can be elicited. Physical examination contributes data on the status of health, development, nutrition, fever, cyanosis, rales, and signs of disease in the heart and lungs. Tests of pulmonary function, reaction of blood and skin to antigens, smears, cultures, and cytology can be crucial in the final diagnosis or can at least exclude a host of diseases.

Both the attending physician and the radiologist appreciate the prevalence of various diseases in their own community, the country, and the world. This appreciation stems from experience, from the literature, and from reports of health authorities. Consciously or subconsciously, excessive rarity, or a high incidence of a disease in a community influences diagnostic judgment. Physicians in the San Joaquin Valley are alert to the possibility of coccidioidomycosis in a case with disseminated lung disease. Certainly paragonimiasis would not be considered often in the United States whereas in the Philippines greater emphasis would be placed on such an infestation.

The contribution of the radiologist in the diagnosis of disseminated lung disease is occasionally definitive but more often puts strong and graded valences on the probability of a few pathogenic agents.

How does the radiologist organize the information on the chest film? The assumption must be made that an abnormal Roentgen pattern is visible; a disseminated disease can exist without manifesting itself on the conventional chest film. One example is an early stage of miliary tuberculosis when the lesions are less than 2 mm. in diameter.

A systematic interpretation of the film should include: (1) description of lesions; (2) anatomical localization; (3) pathologic process; (4) pathogenesis and route of dissemination; (5) differential diagnosis; and (6) recommendation for further study.

DESCRIPTION OF LESIONS. In a detailed description of the lesions one should include the number, size, density, and margin of the average units or components which in the aggregate make up the disseminated pattern. The basic lesion may be radiopaque or more dense than soft tissue, radiolucent or less dense than soft tissue, or have a density equal to soft tissue.

DENSITY GREATER THAN SOFT TISSUE. Lesions with densities greater than soft tissue can be further subdivided into those that are greater than calcific den-

sity and those that are equal to calcific density. The very fact that a lesion is unusually radiopaque or denser than ordinary calcium compounds has important chemical, pathologic, and diagnostic significance. The most striking, radiopaque lesions are caused by compounds of barium, bismuth[56], tin, and iodine. Iron and calcium compounds are somewhat less opaque but are greater than soft tissue density. The presence of calcium most often means calcification from a healing or healed granulomatous process (tuberculosis, histoplasmosis). Very old calcification may be converted to the trabecular pattern of ossification. (Calcifications and ossifications associated with mitral valvular disease.) One tumor is capable of producing disseminated osteoid more or less mineralized in the lungs, metastatic osteogenic sarcoma. There are certain slowly growing, indolent metastatic neoplasms which are denser than normal and therefore must be rich in calcium. These relatively rare chronic, metastatic carcinomas usually arise from the thyroid gland, the salivary gland, or biliary tract. If one suspects that the slightly stippled increased densities are due to iron, then the differential diagnosis contracts to idiopathic hemosiderosis, hemosiderosis associated with mitral disease, or exogenous siderosis (welder's lungs). Thus, it can be seen that from the recognition of increased density, many valid conclusions can be drawn concerning the probable type of pathologic process, probable pathogenesis, route of dissemination and the differential diagnosis.

DENSITY LESS THAN SOFT TISSUE. Radiolucent lesions which have a density less than soft tissue can be described roughly according to size, thickness of rim, and margin. These lesions are generally cavitary[67], cystic, honeycombed, or reticular. The reticular lesion is one that has the pattern of a fine mesh and may be considered to be numerous tiny radiolucencies surrounded by a network of soft tissue density. A reticular lesion is the opposite or "negative" of a stippled lesion which is formed by small specks or dots of increased density against a background of radiolucent lung tissue.

DENSITY EQUAL TO SOFT TISSUE. Disseminated lesions equal to soft tissue density are most frequently encountered and are more difficult to characterize. Many descriptive terms are used with connotations concerning size, shape, and definition. Lesions whose substance and margins are ill-defined are generally described as mottled, patchy, or fluffy. Homogeneous lesions are usually large and have considerable substance. A butterfly pattern has been popularized because it has the appearance of the wings of a butterfly extending from the hilar regions into the central zone of the lungs.

Well-defined lesions may be described as spherical, nodular, miliary and stippled. These descriptions carry with them the connotation of size. Roughly the stippled lesion would be 2 mm.; miliary lesions 4 mm., nodular lesions approximately 6 mm., and the spherical lesion would probably be more than 10 mm. Other lesions that are more linear in shape and usually fairly well-defined may be described as beaded, linear, striated, stranded, or increased markings.

ANATOMICAL LOCATION OF LESION[76]. When the lesions are adequately described as to size, shape, number, and substance the next question to resolve is the anatomical location in the most refined manner possible. There are 3 major anatomical locations: (1) bronchoalveolar tract, (2) vascular system, (3) reticuloendothelial interstitial system.

The bronchoalveolar tract can be

divided into the lobar bronchi, segmental bronchi, subsegmental bronchi, and bronchioles. The respiratory bronchiole is the pathway to the primary lobule which can be further subdivided into the alveolar duct, atria, alveolar sac, and alveolus.

The vascular system in the lung consists of the blood vessels and the lymphatic vessels. The blood vessels are of two kinds: the pulmonary vessels and the bronchial arteries. The pulmonary vessels can be subdivided into the pulmonary arteries, arterioles, capillaries, venules, and veins. Deep in the lungs the lymphatic vessels are disposed over the surface of the blood vessels and bronchi. Lymphatics are present at the atria but not around the alveoli. Toward the hilus the lymphatics form a thick radiating network.

From the entire right lung and from the left lower lobe the lymphatic pathway leads to the right lymphatic duct which empties into the right subclavian vein. From the left upper lobe, lymph goes through the thoracic duct to empty into the left subclavian vein. A superficial pleural plexus passes directly to the hilar nodes by way of the interlobular and lobar connective tissue septa. This plexus receives branches from the deep lymphatic system. The subpleural interlobular connective tissue septa abut the visceral pleural in a perpendicular manner. They are rich in lymphatics. When these lymphatics are engorged or blocked, the interlobular septa become visibly thickened (Kerley's B lines).

If one could remove the entire bronchoalveolar tract and the vascular system, the remaining substance would be the reticuloendothelial interstitial system. This system is rich in macrophages which can travel into and out of the alveoli. It is also rich in lymphoid tissue; the lobules of the lung have aggregations of lymphoid and reticulum cells usually located at the bifurcation of the bronchioles. Small lymph follicles are closer to the hilus and large nodules or nodes of lymph tissue are even more proximal. This system communicates with the hilar, bronchial, and tracheal nodes through lymphatics. The interstitial component is merely the connective tissue and septa which bind together the various systems.

For the sake of brevity this reticuloendothelial interstitial system will from now on be called the "interstitial system."

PROBABLE PATHOLOGY. Inferences concerning the probable pathology of disseminated lesions are not necessarily accurate, but despite obvious limitations the radiologist should strive to form an opinion concerning the nature of the pathologic alterations. Just as gross inspection of the lung may give valid clues to the true pathologic character of lesions so does the Roentgen pattern give clues to gross pathological manifestations as they are translated to the film by ionizing radiation.

Basic pathological processes are inflammation and neoplasm. In the lung inflammatory processes tend to infiltrate and neoplastic processes tend to expand. Inflammation produces exudates and proliferative reactions. Proliferative reactions may give rise to granulation, fibrosis, caseation, necrosis, and calcification.

Ill-defined, mottled, patchy, and fluffy lesions are frequently exudates but cannot be distinguished from transudates, blood, or any other type of fluid. Well-defined lesions are more likely to be due to proliferation, granulation, caseation, or calcification. The radiopacity of calcification renders it fairly easy to identify on a roentgenogram. Linear, striated, and stranded lesions are apt to be fibrotic.

PATHOGENESIS AND ROUTE OF DISSEMI-

NATION. If one could imagine a series of chest films taken at short intervals during the development of the disseminated lung disease or better still a time-lapse cine-roentgenographic study, it would be possible to gain considerable insight into the pathogenesis. Acute diseases often manifest themselves by fuzzy ill-defined lesions of exudative and labile character[27] in contrast to chronic lesions which have sharp well-defined borders. Proliferative lesions heal by fibrosis which slowly contracts and exerts a pull on the lobes, fissures, bronchi, and blood vessels so that the normal anatomical position is displaced.

BRONCHOALVEOLAR SYSTEM. When a disease begins in the bronchi, it may not influence the movement of air in or out and conventional roentgenograms would appear normal. If the disease partially plugs a bronchus so that the check-valve plug allows more air in than out, the portion of lung supplied by that bronchus expands. A bleb is probably an over expanded subpleural lobule of lung produced by partial blockage of a subpleural bronchiole. Numerous blebs produce a coarse rather hexagonal honeycombed pattern. Bullae are similar to blebs but larger and deeper. With greater tension, pneumatoceles are formed and still more intra-alveolar pressure produces the "vanishing lung."

When a bronchus is completely occluded, the gas is quickly absorbed and that portion of lung distal to the occlusion collapses and becomes atelectatic.

Over-expanded lobules (emphysema) and collapsed lobules (atelectasis) mingled with each other would indicate incomplete and complete obstruction of the bronchioli. Hyaline membrane disease, cystic fibrosis (mucoviscidosis), dysautonomia, acute bronchiolitis, and asthmatic pneumonitis[28] are examples of this combination of bronchiolar check valve and complete obstruction. Bronchiolitis obliterans is a fibrotic end stage of bronchiolitis.

The displacement of alveolar air by exudation produces the homogeneous lobar or segmental pattern of pneumonic consolidation. When the lungs become solidified, the gas in the bronchi is revealed like radiolucent twigs. Mottled, patchy, fluffy lesions are subsegmental and lobular consolidations. When a primary lobule is airless, it is occasionally called a rosette because it conforms to the shape of alveolar saccules. Cavities result from tissue necrosis with a pathway of communication to the bronchial tree. Cysts are generally epithelial lined spaces and may be congenital or acquired.

BLOOD VESSELS[5]. Blood vessels react to disease processes by dilatation, increased permeability, or occlusion. Vascular dilatation is the response to increased pressure or flow, or both. Polycythemia has an increased blood volume, anemia has increased flow, and congenital heart disease with a left to right shunt has an increased flow or pressure, or both. Pregnancy produces vascular dilatation because of an increased blood volume and a high diaphragm. Normal physiological states such as expiration or the Mueller maneuver (forced inspiration against a closed glottis) decrease alveolar pressure and can cause a surprising degree of vascular dilatation.

VASCULAR OCCLUSION[47,115]. Totally occluded blood vessels from thrombi or emboli have a tendency to dilate proximally and contract distally. A total occlusion of branches of the pulmonary arteries with or without a factor which compromises the bronchial circulation, may produce infarcts from necrosis and exudation of blood into those portions of the lung supplied by these vessels. Infarcts generally are peripheral and basilar in distribution. Frequently two visceral pleural or fissural surfaces, or both, are involved. The shape of the

lung involved is a truncated pyramid because the top usually received a collateral blood supply. Frequently this configuration is difficult to recognize with the usual projections. In vessels which are partially and sharply obstructed by a stenosis or coarctation there is tendency to develop not only proximal dilatation but also poststenotic dilatation.

PERIVASCULAR FLUID. Fluid such as serum or plasma accumulates around vessels when there is an increased production of fluid, a decreased absorption or transport of fluid or an increased vascular permeability. These factors may operate singly or in combinations. Small amounts of perivascular fluid blur the vascular margins; large amounts obliterate the margins.

When pulmonary venous pressure is increased by heart failure, or other conditions, there is a transudation of protein poor fluid which gives the pattern of passive congestion. A decreased osmotic pressure of blood from loss of protein (nephrosis) can also produce transudation. Aggravated passive congestion becomes pulmonary edema which characteristically has a central lobar and often a butterfly distribution.

If the disease process damages the vascular endothelium, increasing permeability would allow not only albumin to escape but also exudates with globulin and fibrinogen and even red and white blood cells. Anoxia, toxins, antigen-antibody reactions[101,104] and collagen vascular disease often produce a vasculitis which may be focal, disseminated, or generalized.

The patterns produced by collagen vascular diseases depend largely upon the size, extent, degree, and chronicity of vascular involvement. Polyarteritis nodosa frequently involves seriously and acutely the larger arteries and arterioles in the heart and lung. Focal lung necrosis and granulomas may form (Wegener's granulomatosis).

Systemic lupus erythematosus usually involves smaller vessels in a more

TABLE 2.—DISSEMINATION OF LUNG DISEASE

A Systematic Classification of Etiologies

Route of Dissemination *Respiratory Tract*	*Route of Dissemination* *Circulatory System*
	Pulmonary Artery Embolization
Bacterial	*Bacterial*
See also bacterial agents listed under circulatory system.	See also bacterial agents listed under respiratory tract.
Tuberculosis, primary and reinfection	Tuberculosis (miliary)
Staphylococcus	Salmonella
Streptococcus	Tularemia
Pneumococcus	Staphylococcus (septic emboli)
Friedlander pneumonia	Streptococcus (hematogenous abscesses)
Pertussis	Leptospirosis
Melioidosis, glanders	
Plague	
Bronchopneumonia	
Fuso-spirochetal infection	
Fungi	*Fungi*
See also those listed under Circulatory system	See also those listed under respiratory tract
Actinomycosis	Histoplasmosis
Nocardiosis	Blastomycosis
Geotrichosis	Coccidioidomycosis
Sporotrichosis	
Cryptococcosis	*Rickettsia*
Moniliasis	Rocky Mountain spotted fever
Aspergillosis	Q fever

TABLE 2.—*(Continued)*

Virus

Atypical pneumonia
Ornithosis
Psittacosis
Varicella, chickenpox
Rubeola, measles
Infectious mononucleosis
Cytomegalic inclusion disease

Neoplasm

Bronchiolar carcinoma
Pulmonary adenomatosis
Alveolar cell carcinoma

Aspiration

Hemorrhage
Drowning
Lipoid
Esophageal disease, fistula, obstruction, diverticulum
Neurologic swallowing defect
Foreign bodies
Lipiodol

Inhalation, gases

Acetylene
Mustard gas
Nitrogen dioxide NO_2
Silo-filler's disease (NO_2)
Phosgene
Sulfur dioxide (SO_2)
Steam, hot air

Pneumoconiosis, organic

Bagassosis (bagasse)
Byssinosis (cotton lint)
Tobaccosis (tobacco)

Pneumoconiosis, inorganic inert

Anthracosis (coal)
Graphite (carbon)
Siderosis (iron)
Baritosis (baryta)
Stannosis (tin)

Pneumoconiosis, inorganic proliferative

Beryllosis (beryllium)
Silicosis (silica)
Asbestosis (silicates)

Parasites

Amebiasis
Toxoplasmosis
Pneumocystis carinii ?(plasma cell pneumonia)
Ascariasis
Visceral Larva migrans
Paragonimiasis
Schistosomiasis
Filariasis
Cysticercosis
Echinococcosis
Porocephalosis

Neoplasm

Carcinoma (metastatic)
Sarcoma (metastatic)

Physical and Chemical Agents

Multiple aseptic emboli
Fat emboli
Amniotic fluid
Metallic particles (traumatic)
Barium (iatrogenic)
Lipiodol (iatrogenic)[105]

Liquids probably exhaled from bloodstream

Kerosene
Turpentine
Carbon tetrachloride
Gasoline
Lighter fluid

Lymphatic Spread, Carcinoma

Lung
Breast
Stomach
Pancreas
Colon
Biliary tract
Kidney

subtle and chronic process. Scleroderma usually affects very small vessels in a low grade, very chronic fashion with the production of much fibrosis[37]. The authors believe that such entities as farmer's lung, pulmonary alveolar proteinosis, idiopathic pulmonary hemosiderosis, and rheumatic pneumonitis have the same pathogenesis as the collagen vascular diseases.

In certain cases of rheumatic mitral heart disease with chronic passive congestion blood from dilated venules will ooze into the interstitial system. Macrophages will degrade the hemoglobin to hemosiderin and coalesce the particles within the reticuloendothelial network. Calcium deposits in these areas which are rich in hemosiderin and eventually ossification occurs.

INTERSTITIAL SYSTEM. A number of disease entities originate in the reticuloendothelial tissues of the lung. Examples are the lipoid storage diseases: Hand-Schüller-Christian, histiocytosis X or eosinophilic granuloma. Lymphomas may originate in the lung but more often arise in the hilar and mediastinal nodes. Sarcoidosis and amyloidosis certainly involve the reticuloendothelial system, but their true etiologies are not known. The etiology of interstitial fibrosis of Hamman-Rich syndrome is not known: it may well be caused by a variety of pathogens.

ROUTE OF DISSEMINATION. The final location of many pathogens is in the reticuloendothelial and interstitial tissue. It should be realized that there is a slow route of communication between the bronchoalveolar and vascular system by way of the interstitial system. With increasing age, dust, particularly carbon (anthracosis), will lodge in the interstitial system and cause increased reticular and linear markings from fibrosis. The lymphatics form a faster channel of distribution of pathogens. The fastest and primary channels of distribution of pathogens are the bronchoalveolar system and the blood vascular system. These two systems are the main routes of transportation and dissemination of a multitude of pathogenic agents (Table 2).

BRONCHOALVEOLAR SPREAD. It is natural with lung disease that the main port of entry of pathogens is through the larynx. The respiratory tract has many special characteristics which govern the entry and dissemination of disease. The filtering action of nasal hairs, the cleansing action of ciliated epithelium and the cough reflex guard against daily attacks from ubiquitous pathogens. Individuals not only differ from each other in protective mechanisms but also a person can change from time to time.

The right mainstem bronchus is slightly larger and more vertical than the left. These facts explain why aspirated materials are directed into the right lung more often than the left. However, age, body position, debility, dentures, neurological states, esophageal diseases, and the nature of the material influence the dissemination and pattern of aspirated materials[4]. The factors which play an important role in the dissemination and pathogenesis of dust diseases (pneumoconiosis) are concentration, size, and nature of the particles. To be inhaled most particles must be below 10 microns in size. Organic particles such as bagasse, cotton linters and tobacco are probably allergens. Carbon, barium, bismuth, and tin are relatively inert and produce a low grade fibrosis. Silica and beryllium produce a more damaging proliferative reaction. Chronic beryllosis mimics the reticuloendothelial, hilar node pattern of sarcoidosis. The heavy silicate fibers of asbestosis are found at the bases of the lungs while the smaller silica particle diffuses more generally and then gradually contracts toward the hilum because of fibrosis and migration. "Eggshell" calcification[41], in the lymph nodes, is characteristic of some cases of advanced silicosis. The inhalation of irritant gases produces a bronchiolitis. Inhalation of infectious agents generally produce a pneumonitis. Figure 1 is a case of aspiration pneumonitis which demonstrates a pattern of bronchoalveolar spread of disease.

VASCULAR SPREAD. The vascular spread

of disease is not so common as bronchoalveolar spread. The portals of entry into the circulatory system can be through the respiratory tract, skin or gastrointestinal tract. Pathogens in the respiratory tract can erupt into blood vessels or migrate through the lymphatic system.

The true miliary pattern of distinct, widespread, uniform, and usually numerous lesions in the lung is usually due to a blood-borne pathogen. The extreme periphery of the lung is often spared. The pure miliary pattern is most often caused by tuberculosis, histoplasmosis, other fungus infections,

Fig. 1.—*Bronchoalveolar dissemination. Aspiration pneumonitis,* 12-year-old white girl with quadraplegia since age of 30 months. Clinically she had episodes of fever; cough due to aspiration of ingested material. Necropsy revealed chronic pneumonitis with foreign body reaction.

TABLE 3.—DISSEMINATED LUNG DISEASE BY ANATOMICAL LOCATION

Primary Involvement of Bronchial Tree	*Primary Involvement of Blood Vessels*
Chronic bronchitis	Arteriovenous fistulae
Bronchiectasis	Passive congestion
Bronchiolitis	Pulmonary edema
Bronchiolectasis	Hemosiderosis (mitral)
Bronchiolitis obliterans	Polyarteritis nodosa
Cystic fibrosis (mucoviscidosis)	Wegener's granuloma
Dysautonomia (Riley-Day)	Systemic lupus erythematosus
Atelectasis	Scleroderma
Hyaline membrane disease	Farmer's lung
Congenital cystic disease[8]	Pulmonary alveolar proteinosis
Blebs, bullae	Idiopathic pulmonary hemosiderosis
Pneumatoceles, Vanishing lungs	Rheumatic pneumonitis
Emphysema	Tropical eosinophilia
Fibrocystic disease	Erythema nodosum
Tuberous sclerosis	Concussion, blast
Bronchogenic carcinoma	
Pulmonary microlithiasis	

TABLE 4.—CIRCULATORY SYSTEM, MORPHOLOGIC CHANGES

Vascular Dilatation	*Lymphatic Dilatation*
Anemias, sickle, Cooley's	Mitral Disease (Kerley's B lines)
Leukemia	Hemosiderosis
Polycythemia vera	Pneumoconiosis
Congenital heart (left to right shunt)	Infection
Pregnancy	Neoplasm[38]
Expiration film, Mueller maneuver	

TABLE 5.—MISCELLANEOUS, DISSEMINATED LUNG DISEASE

UNKNOWN—UNDIAGNOSED

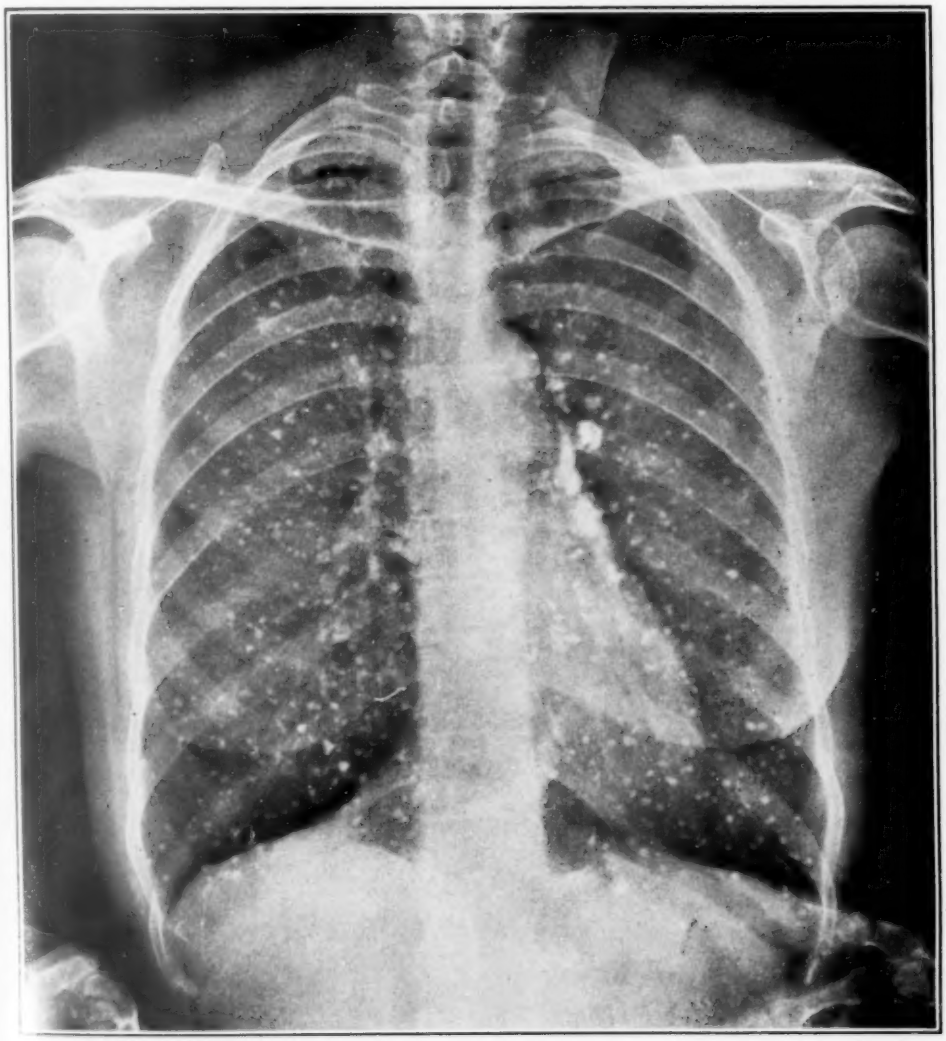
Reticuloendothelial Tissue	*Erroneously Believed Lung Disease*
Letterer-Siwe's disease	Rachitic rosary, ribs
Hand-Schüller-Christian disease	Scorbutic bayonet, ribs
Histiocytosis X	Fractures, ribs
Eosinophilic granuloma	Porotic folded fractures
Gaucher's disease	Multiple myeloma
Sarcoidosis	Osteochondromas
Amyloidosis	Osteopoikilosis
Hodgkin's disease	Osteoblastic metastases
Reticulum cell sarcoma	Neurofibromatosis
Lymphoma	Artefacts

Interstitial Tissue

Interstitial fibrosis, Hamman-Rich syndrome
Fibrosis

and metastatic neoplasms. Figure 2 is a case of healed histoplasmosis. The organism was disseminated by the blood stream.

Metastatic tumors which spread through the blood vessels are often sparse in number[68], spherical in shape, and variable in size. For some unknown reason early lesions tend to localize in the posterior segments of the lower lobes. Some radiologists believe that metastatic sarcomas produce more sharply defined, perfect spheres than carcinomas.



ig. 2.—*Blood-borne disease. Healed histoplasmosis.* Fifty-three-year-old white woman with o symptoms referable to her chest. Tuberculin skin tests were negative, histoplasmin positive. his finding of disseminated calcification is common in areas where histoplasmosis is endemic.

Septic emboli or pyemias produce septic infarcts or hematogenous abscesses. They also are prone to be few in number. They usually cavitate and have indistinct margins. These blood-borne abscesses may heal completely or leave a fibronodular scar[40]. In its early stages metastatic choriocarcinoma can mimic septic emboli because of its tendency for hemorrhage and necrosis.

Infestation of the lung is usually blood-borne and the acute allergic component produces an exudative fuzzy margin. The cycles of many parasites

Fig. 3.—*Lymphatic dissemination of disease. Carcinoma of breast with lymphatic borne lung metastases.* Fifty-three-year-old-white woman who had right radical mastectomy 5 years ago. The film reveals widespread bilateral pulmonary infiltrate and enlargement of the hilar areas.

are quite complex. For example, ascaris penetrates the bronchoalveolar tree, ascends to the epiglottis and enters the gastrointestinal tract. Strongyloides and Paragonimus can produce cavities.

The pathogenesis of disease caused by kerosene and similar hydrocarbon liquids is not definitely established. The evidence favors the theory that after they are ingested they are carried to the lung by the blood stream and then the volatile fraction is exhaled. Both the basilar blood vessels and the bronchoalveolar tract may show signs of irritation and inflammation.

The lymphatic spread to the lung of carcinoma forms a rather distinctive beaded pattern radiating from the hilus. The most common origins of these carcinomas are lung, breast, stomach, pancreas, biliary tract, colon, and kidney in this order of occurrence. Figure 3 is a case of metastatic carcinoma of the breast which demonstrates lymphatic spread.

DIFFERENTIAL DIAGNOSIS. When all the facts and inferences are mustered, the differential diagnosis is still difficult but more readily managed. If the description, localization, pathology, pathogenesis and route of dissemination are clear the general type of disease entity or pathogen can often be suggested.

In the objective analysis of the chest roentgenogram, it is legitimate to weigh every bit of ancillary evidence. The abnormal size or shape of the heart and great vessels, the appearance of the skin, soft tissues, breasts, bones, diaphragm, and spleen can furnish important clues. Certainly a deviated trachea, the presence of pleural fluid or the enlargement of the mediastinal nodes may influence a diagnostic opinion.

It is important to keep in mind that two or more diseases may coexist[69]. Sometimes these diseases are merely coincidental but often one disease process exerts a deleterious influence on the other. Tuberculosis and fungus infection can be engrafted on carcinoma, collagen vascular disease, or blood dyscrasia. Any two or more of the following diseases can coexist: Silicosis, tuberculosis, fungus infection, collagen vascular disease, carcinoma, blood dyscrasia, myeloma and leukemia. Antibiotic and steroid therapy may also play a role.

RECOMMENDATIONS FOR FURTHER STUDY. The simple repeat chest film, the lateral, obliques, and the fluoroscope can rule out artefacts and extrapulmonary diseases. Such entities as rib fractures, osteopoikilosis and neurofibromata may on occasion cause difficulty. The follow-up film can arbitrate an acute or chronic process. When indicated the modern radiologist does not hesitate to use more specialized procedures such as: inspiration-expiration films, Valsalva or Mueller maneuver, grid or Bucky films, recumbent positions, stereoscopic films, body section, and super voltage films. Highly specialized examinations, bronchography, angiocardiography and cineradiography may be of great value in differential diagnosis.

Summary. In the problem of differential diagnosis of disseminated lung disease the radiologist can frequently help the attending physician by a thorough analysis of the Roentgen pattern according to the following outline:

1. Description of Lesion: size, shape, number, density
2. Anatomical Localization: bronchoalveolar, vascular, interstitial
3. Pathologic process: inflammatory, neoplastic
4. Pathogenesis and route of dissemination: bronchoalveolar, vascular, interstitial
5. Differential Diagnosis
6. Recommendations for further study

ACKNOWLEDGMENT: The authors wish to express their appreciation to Dr. Harold M. Landsman for his counsel and helpful criticism.

REFERENCES

(1) **Arendt, J.:** Am. J. Roentgenol., **64,** 950, 1950. (2) **Ariztia, A., Bustamante, W., Moreno, L.,** and others: J. Pediat., **51,** 639, 1957. (3) **Austrian, C. R.,** and **Brown, W. H.:** Am. Rev. Tuberc., **45,** 751, 1942.

(4) **Baker, G. L.,** and **Heublein, G. W.:** Am. J. Roentgenol., **80,** 42, 1958. (5) **Barden, R. P.,** and **Cooper, D. A.:** Ibid., **61,** 17, 1949. (6) **Beerman, H.:** Am. J. Med. Sci., **223,** 433, 1952. (7) **Birsner, J. W.:** Am. J. Roentgenol., **72,** 556, 1954. (8) **Brantigan, O. C.:** Dis. Chest., **15,** 192, 1949. (9) **Bruwer, A. J., Kennedy, R. L. J.,** and **Edwards, J. E.:** Am. J. Roentgenol., **76,** 98, 1956. (10) **Bruwer, A. J., Kierland, R. R.,** and **Schmidt, H. W.:** Ibid., **75,** 748, 1956.

(11) **Campbell, J. A.,** and **Silver, R. A.:** Radiology, **61,** 161, 1953. (12) Case Records of the Massachusetts General Hospital. Case #43021: New England J. Med., **256,** 79, 1957. (13) **Chapple C. C.:** J. Am. Med. Assn., **166,** 619, 1958. (14) **Corcoran, W. J.:** Radiology, **50,** 751, 1948. (15) **Cummings, M. M.,** and **Hudgins, P. C.:** Am. J. Med. Sci., **236,** 311, 1958.

(16) **DeCarlo, J., Jr.,** and **Startzman, H. H., Jr.:** Radiology, **63,** 849, 1954. (17) **Dennis, J. M.,** and **Boudreau, R. P.:** Ibid., **68,** 25, 1957. (18) **Dickie, H. A.,** and **Rankin, J.:** J. Am. Med. Assn., **167,** 1069, 1958. (19) **Doniach, I.:** Am. J. Roentgenol., **58,** 620, 1947. (20) **Doub, H. P., Goodrich, B. E.,** and **Gish, J. R.:** Ibid., **71,** 785, 1954. (21) **Dundon, C. C.,** and **Hughes, J. P.:** Ibid., **63,** 797, 1950.

(22) **Emery, J. L.,** and **Lorber, J.:** Brit. Med. J., **2,** 702, 1950. (23) **Esposito, M. J.:** Am. J. Roentgenol., **73,** 351, 1955.

(24) **Farber, S. M.,** and **Wilson, R. H. L.:** Clin. Sympos., **10,** 171, 1958. (25) **Favour, C. B.,** and **Sosman, M. C.:** Arch. Int. Med., **80,** 435, 1947. (26) **Feci, L.:** Radiol. Med., **20,** 620, 1933. (27) **Felson, B.:** Radiology, **59,** 32, 1952. (28) **Felson, B.,** and **Felson, H.:** Am. J. Roentgenol., **74,** 235, 1955. (29) **Felson, H.,** and **Heublein, G. W.:** Ibid., **59,** 59, 1948. (30) **Fisher, E. R.,** and **Davis, E.:** New England J. Med., **258,** 1036, 1958. (31) **Fleischner, F. G.:** Radiology, **53,** 818, 1949. (32) **Fleischner, F. G.,** and **Berenberg, A. L.:** Ibid., **62,** 522, 1954. (33) **Foley, J. C., Dreyer, N. B., Soule, A. B., Jr.,** and **Woll, E.:** Ibid., **62,** 817, 1954. (34) **Frank, R. C.:** Am. J. Roentgenol., **79,** 189, 1958. (35) **Furcolow, M. L.:** Pub. Health Rep., **64,** 1363, 1949.

(36) **Garland, L. H.:** Radiology, **48,** 333, 1947. (37) **Garland, L. H.,** and **Sisson, M. A.:** Am. J. Roentgenol., **71,** 581, 1954. (38) **Giammalvo, J. T.,** and **Jones, S. H.:** Dis. Chest, **34,** 337, 1958. (39) **Gould, D. M.,** and **Torrance, D. J.:** Am. J. Roentgenol., **73,** 366, 1955. (40) **Grayson, C. E.:** Ibid., **62,** 208, 1949. (41) **Grayson, C. E.,** and **Blumenfeld, H.:** Radiology, **53,** 216, 1949. (42) **Greening, R., Kynette, A.,** and **Hodes, P. J.:** Am. J. Roentgenol., **77,** 1059, 1957. (43) **Greenspan, R. H.,** and **Feinberg, S. B.:** Radiology, **68,** 860, 1957. (44) **Gundersen, G. A.,** and **Nice, C. M., Jr.:** Ibid., **68,** 31, 1957.

(45) **Hamman, L.,** and **Rich, A. R.:** Bull. Johns Hopkins Hosp., **74,** 177, 1944. (46) **Hampton, A. O., Bickham, C. E., Jr.,** and **Winship, T.:** Am. J. Roentgenol., **73,** 938, 1955. (47) **Hanelin, J.,** and **Eyler, W. R.:** Radiology, **56,** 689, 1951. (48) **Hardy, J. B.:** Vol. 1. Tuberculosis in White and Negro Children. Roentgenologic aspects of the Harriet Lane Study. Cambridge: Published for the Commonwealth Fund by Harvard University Press, 1958. (49) **Haubrich, R.,** and **Schuler, B.:** Fortschr. Geb. Rontgenstrahlen, **78,** 272, 1953. (50) **Hawley, C.,** and **Felson, B.:** Am. J. Roentgenol., **75,** 751, 1956. (51) **Henderson, A. T.,** and **Peirce, C. B.:** Ibid., **58,** 391, 1947. (52) **Hendren, W. H., III,** and **Haggerty, R. J.:** J. Am. Med. Assn., **168,** 6, 1958. (53) **Hood, R. M., O'Connell, H. V.,** and **McCord, D. L.:** Am. Rev. Tuberc., **78,** 21, 1958. (54) **Humphrey, A. A.,** and **Olmstead, E. G.:** Dis. Chest, **15,** 471, 1949. (55) **Hyde, L., Hyde, B.,** and **Pokorny, C.:** Ibid., **19,** 190, 1951.

(56) **Jackson, C.:** Am. J. Roentgenol., **5,** 454, 1918. (57) **Jacobs, L. G.:** Radiology, **71,** 398, 1958. (58) **Jacobs, L. G., Gerstl, B., Hollander, A. G.,** and **Berk, M.:** Ibid., **67,** 527, 1956. (59) **Joress, M. H.,** and **Bushueff, B. P.:** New England J. Med., **254,** 1053, 1956; **255,** 359, 1956.

(60) **Kalmon, E. H.:** Radiology, **62**, 222, 1954. (**61**) **King, D. S.:** Internat. Clin., **1**, 115, 1938. (**62**) **Knights, E. M., Jr., Brush, J. S.,** and **Schroeder, J.:** J. Am. Med. Assn., **169**, 1279, 1959. (**63**) **Kobernick, S. D.:** Am. J. Med. Sci., **224**, 329, 1952. (**64**) **Kornblum, D.,** and **Fineberg, R.:** Am. J. Roentgenol., **74**, 587, 1955. (**65**) **Kritchman, M. M., Schwartz, H.,** and **Papper, E. M.:** J. Am. Med. Assn., **170**, 529, 1959. (**66**) **Krugman, S., Goodrich, C. H.,** and **Ward, R.:** New England J. Med., **254**, 843, 1957.

(67) **Laforet, E. G.,** and **Laforet, M. T.:** Dis. Chest, **31**, 665, 1957. (**68**) **Lampe, I.,** and **Zatzkin, H.:** Radiology, **53**, 379, 1949. (**69**) **Longo, L. B., Harbuck, A. B.,** and **Fleischmann, W.:** Dis. Chest, **33**, 398, 1958. (**70**) **Lowry, T.,** and **Schuman, L. M.:** J. Am. Med. Assn., **162**, 153, 1956.

(71) **Machle, W.:** Radiology, **50**, 755, 1948. (**72**) **Mallory, T. B.:** Ibid., **51**, 468, 1948. (**73**) **Mayer, E.,** and **Rappaport, I.:** Dis. Chest, **21**, 146, 1952. (**74**) **Meszaros, W. T.:** Radiology, **70**, 313, 1958. (**75**) **Miller, F. L.,** and **Walker, R.:** Ibid., **65**, 231, 1955. (**76**) **Miller, W. S.:** The Lung, 2nd ed. Springfield, Ill.: Charles C Thomas, 1947. (**77**) **Moloshok, R. E.,** and **Moseley, J. E.:** Pediatrics, **17**, 327, 1956. (**78**) **Morris, G. L.,** and **Yates, J. L.:** Dis. Chest, **30**, 298, 1956. (**79**) **Myers, B.:** Brit. Med. J., **2**, 8, 1937.

(80) **Oderr, C. P.,** and **Shaw, J. F.:** Am. J. Roentgenol., **76**, 94, 1956. (**81**) **O'Leary, D. J.,** and **Curry, F. J.:** Am. Rev. Tuberc., **73**, 501, 1956. (**82**) **Oliphant, J. W.,** and **Parker, R. R.:** Pub. Health Rep., **63**, 1364, 1948. (**83**) **Opie, L. H.:** Dis. Chest, **28**, 665, 1955.

(84) **Pagan-Carlo, J.,** and **Haley, T. J.:** Am. J. Roentgenol., **81**, 231, 1959. (**85**) **Parsons, R. J.,** and **Zarafonetis, C. J. D.:** Arch. Int. Med., **75**, 1, 1945. (**86**) **Pendergrass, E. P.:** Am. J. Roentgenol., **80**, 1, 1958. (**87**) **Pendergrass, E. P.,** and **Robert, A. G.:** Radiology, **50**, 725, 1948. (**88**) **Post, G. W., Jackson, A., Garber, P. E.,** and **Veach, G. E.:** Dis. Chest, **34**, 455, 1958.

(89) **Reed, E. S., Wells, P. O.,** and **Wicker, E. H.:** Radiology, **71**, 661, 1958. (**90**) **Renzetti, A. D., Jr., Eastman, G.,** and **Auchincloss, J. H., Jr.:** Am. J. Med., **22**, 834, 1957. (**91**) **Rigler, L. G.:** The Chest; A Handbook of Roentgen Diagnosis. 2nd ed. Chicago: Year Book Publishers, 1954. (**92**) **Robbins, L. L.:** Am. J. Roentgenol., **51**, 459, 1948. (**93**) **Robert, A. G.:** Ibid., **63**, 467, 1950. (**94**) **Rogers, J. V., Jr.,** and **Roberto, A. E.:** Ibid., **76**, 88, 1956. (**95**) **Rosen, B.:** Radiology, **65**, 373, 1955. (**96**) **Rosen, S. H., Castleman, B.,** and **Liebow, A. A.:** New England J. Med., **258**, 1123, 1958. (**97**) **Rubin, E. H.,** and **Lubliner, R.:** Medicine, **36**, 397, 1957. (**98**) **Russo, P. E.,** and **Cavanaugh, C. J.:** Radiology, **60**, 198, 1953.

(99) **Sander, O. A.:** Am. J. Roentgenol., **58**, 277, 1947. (**100**) **Sante, L. R.:** Ibid., **62**, 788, 1949. (**101**) **Sante, L. R.,** and **Wyatt, J. P.:** Ibid., **66**, 527, 1951. (**102**) **Scadding, J. G.:** Brit. J. Radiol., **29**, 633, 1956. (**103**) **Schultze, G.:** Am. J. Roentgenol., **81**, 290, 1959. (**104**) **Shapiro, H.,** and **Lowman, R. M.:** Dis. Chest, **32**, 329, 1957. (**105**) **Shapiro, J. H., Rubinstein, B., Jacobson, H. G.,** and **Poppel, M. H.:** Am. J. Roentgenol., **77**, 1055, 1957. (**106**) **Silverstein, C. M.:** Radiology, **61**, 327, 1953. (**107**) **Sochocky, S.:** Dis. Chest, **32**, 335, 1957. (**108**) **Sosman, M. C., Dodd, G. D., Jones, W. D.,** and **Pillmore, G. V.:** Am. J. Roentgenol., **77**, 947, 1957. (**109**) **Southard, M. E.:** Ibid., **76**, 533, 1956. (**110**) **Squier, T. L.:** Dis. Chest, **13**, 609, 1947. (**111**) **Steinbach, H. L.,** and **Johnstone, H. G.:** Radiology, **68**, 234, 1957. (**112**) **Steinberg, I.,** and **McClenahan, J. L.:** Am. J. Med., **19**, 549, 1955. (**113**) **Storey, C. F., Knudtson, K. P.,** and **Lawrence, B. J.:** J. Thoracic Surg., **26**, 331, 1953. (**114**) **Suwanik, R.,** and **Harinsuta, C.:** Am. J. Roentgenol., **81**, 236, 1959.

(115) **Torrance, D. J., Jr.:** Am. J. Med. Sci., **237**, 651, 1959. (**116**) **Tuft, L.,** and **Girsh, L. S.:** Ibid., **235**, 60, 1958.

(117) **Viswanathan, R.:** Dis. Chest, **15**, 460, 1949.

(118) **Wang, C. C.,** and **Robbins, L. L.:** Radiology, **66**, 489, 1956. (**119**) **Webster, B. H.:** Dis. Chest, **30**, 315, 1956. (**120**) Idem: Ibid., **35**, 273, 1959. (**121**) **Weiss, W.,** and **Johnston, D. G.:** Am. Rev. Tuberc., **75**, 319, 1957. (**122**) **Wolfe, J. N.,** and **Jacobson, G.:** Am. J. Roentgenol., **79**, 216, 1958.

(123) **Zarafonetis, C. J. D., Lorber, S. H.,** and **Hanson, S. M.:** Am. J. Med. Sci., **236**, 1, 1958.

THERAPEUTICS

UNDER THE CHARGE OF

HARRY GOLD, M.D.
PROFESSOR OF CLINICAL PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE

AND

McKEEN CATTELL, M.D.
PROFESSOR OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK, NEW YORK

DRUG THERAPY OF GASTROINTESTINAL DISEASE

BY DAVID H. LAW, M.D.
INSTRUCTOR IN MEDICINE

FREDERIC W. SMITH, M.D.
RESEARCH FELLOW IN MEDICINE

GORDON D. BENSON, M.D.
RESEARCH FELLOW IN MEDICINE

AND

MARVIN H. SLEISENGER, M.D.
ASSOCIATE PROFESSOR OF CLINICAL MEDICINE

(From the Department of Medicine, New York Hospital-Cornell Medical Center, New York, New York)

THE appearance of a bewildering number of drugs, attended by great publicity and fanfare, has brought considerable confusion to gastrointestinal therapeutics in recent years. The pharmacological basis for the use of such agents seems to be considered less and less; a placebo effect is mistaken for specific action in numerous instances. Perhaps the most serious shortcoming in the physician's approach to drug treatment is failure to consider, or ignorance of, the patho-physiology of the diseases and disorders with which he deals and the specific pharmacologic actions of the drugs he uses. These observations seem particularly pertinent in the treatment of gastrointestinal ailments.

The purpose of this paper is to review certain aspects of drug therapy of gastrointestinal disorders with reference to these important points. We will not compare various compounds of similar structure and action.

For the sake of convenience and clarity, the conditions to be discussed are divided into 4 categories: diseases and disorders of motility; chronic inflammation of the small and large intestine; peptic ulceration; and the malabsorption states.

1. DISEASES AND DISORDERS OF MOTILITY. Included in this category are: 1) diseases in which motor power, particularly peristalsis, is markedly impaired, due either to deficient intrinsic innervation (cardiospasm; congenital

megacolon) or to marked diminution of smooth muscle action resulting from atrophy and fibrosis (scleroderma); 2) disorders of motility, including functional "dyspepsia" and the irritable colon syndrome.

a. Cardiospasm (Achalasia). In this disease, characterized by dysphagia and variable degrees of esophageal dilatation, there is a serious impairment of motor activity, both in the body of the esophagus and in the terminal vestibular segment, the esophago-gastric sphincter[31,43,73,99,100,161]. As a result, normal peristalsis is replaced by numerous phasic, purposeless contractions of the body. The vestibular segment fails to relax with swallowing and maintains inordinately high pressures. The basis for these disturbances is thought to be the marked diminution or absence of ganglion cells of the myenteric plexuses of the esophagus, particularly the distal 2/3 of the organ[44,104,133].

Although *parasympathomimetic* agents have been used in the treatment of this disorder, they are not able to restore normal function in such patients. Administration of such drugs as methacholine (Mecholyl) or *bethanechol chloride* (Urecholine) causes decrease in the sphincter pressure but leads to marked spasm of the body with much substernal discomfort and no improvement in swallowing[73]. *Anticholinergic* drugs such as atropine and the quaternary ammonium compounds such as propantheline (Probanthine), abolish the uncomfortable "purposeless" or "tertiary" contractions and decrease pressure in the sphincter, but will not improve function since they produce dilatation and atony of the body[73]. *Smooth muscle relaxants,* such as the nitrites (Amyl Nitrite, ampules) will reduce sphincter pressure temporarily, but such decrement is usually followed by a "rebound" rise of pressure to a higher level than was present prior to relaxation. Practical benefit from nitrites, therefore, is limited to relief of the discomfort due to inspissation of meat or other solid food in the distal narrowed segment, and to aid in passing a bougie through the narrowed vestibule.

b. Megacolon (Hirschsprüng's Disease). Since the elucidation of the basic defect in this disease, namely, the diminution or absence of ganglion cells of the myenteric plexuses of the upper rectum and lower sigmoid, the surgical approach is the therapy of choice[165]. However, in a limited number of patients who are poor surgical risks, or who refuse the procedure, management necessarily must be medical.

Use of oral *parasympathomimetic agents* such as *bethanechol chloride* or *methacholine* may be beneficial; however, the dosages required are difficult to regulate and the effective level usually causes troublesome side effects. Nevertheless, 15 to 25 mg. bethanechol chloride by mouth, twice daily, may aid evacuation greatly. The rationale for the use of such an agent lies in its stimulant action upon the proximal dilated colon, permitting propulsion of feces through the undilated, denervated segment. Alternately, *neostigmine bromide,* a cholinesterase inhibitor, may be given orally (15 to 30 mg.) two or three times daily.

Laxatives are also of value and the safest and most commonly employed are the bulk colloids or, if more liquid feces is required, a saline purgative such as *milk of magnesia.* These may be given daily or several times weekly depending upon the needs of the individual patients.

c. Scleroderma. Serious involvement of the gastrointestinal tract, particularly the esophagus, is common in progressive systemic sclerosis[42,140]. The alteration of connective tissue and atrophy of smooth muscle of the gut

is responsible for marked impairment of muscular functions. The resultant diminution or loss of peristalsis leads to varying degrees of atony of the esophagus, small bowel and colon. Commonly, these patients complain of dysphagia and, occasionally, of abdominal distention and severe constipation. Esophagitis with stricture often follows the appearance of a *sliding hiatal hernia* due, probably, to some fibrotic contraction of the esophagus. The motor disturbances of the small intestine, plus secondary mucosal involvement of this organ, rarely may be severe enough to cause a *malabsorption syndrome*[140].

Obviously, drug therapy in this situation is, at best, supportive and symptomatic. Although claims have been made for the efficacy of *para-aminobenzoic acid* (12 gm. q.d.)[179], *corticosteroids* (prednisone or prednisolone, 10 to 20 mg. q.d.)[139], and the hormone, *releasin* (20 to 30 units q.d.)[33,55], in the management of the other systemic manifestations of scleroderma, neither relief of the troublesome gastrointestinal symptoms nor a stemming of the progress of the disease in the gut has been substantiated.

Motility studies of esophagus and small intestine have indicated that a *parasympathomimetic agent,* such as methacholine, alters the basic pattern very little[43,71,99]. Some increase in local phasic activity may occur, but propulsion usually does not improve. Nevertheless, a trial of *bethanechol chloride,* 15 to 20 mg. given orally before meals, may be helpful in an occasional patient, particularly for the relief of distention and for stimulating evacuation. As with the use of corticosteroids, however, close observation must be made for symptoms of peptic ulcer or sliding hiatus hernia with esophagitis. Drug therapy for these conditions should be given as outlined elsewhere in this review.

d. Functional Dyspepsia. For want of a more specific term, this refers to that syndrome which is characterized by a multitude of complaints including heartburn, epigastric heaviness, sourness, bloating, belching, nausea and regurgitation. Emotional tension, eating rapidly, and ingestion of large quantities of food, all may give rise to these symptoms in susceptible individuals. Delayed gastric emptying is presumed to be the basis[156]. Although one would imagine that *parasympathomimetic* drugs, which promote gastric emptying, would benefit these patients, our results with their use have been disappointing. Drug therapy may be of use in this condition, however, and specific symptoms may be alleviated. Heartburn, probably due to lower esophageal irritation by reflux of acid gastric juice, is combated well with antacid medication (see below) taken shortly after eating. Nausea often associated with "dyspepsia" may be offset or prevented by the new antiemetic *phenothiazine* compounds such as Compazine and Dartal, 10 mg. before meals. These compounds appear to exert their influence on chemo-receptors of the vomiting center in the medulla, but also possess varying degrees of peripheral autonomic blocking activity[41,112]. Further indication for the use of these drugs is their beneficial effect upon emotional tension which so often plays an important role in the genesis of these symptoms. In this regard, *phenobarbital* (15 to 30 mg.) likewise may be useful.

e. Irritable Colon (Mucous Colitis; Spastic Colon). This very common condition, characterized by lower abdominal cramping pain, distention, flatulence, and abnormal bowel habits (constipation or diarrhea or both), has been the object of intensive study for

many years[7,8,175]. It is extremely important to realize that the effectiveness of drug therapy in this condition is heavily influenced by the emotional state of the patient, particularly as it becomes molded by the doctor-patient relationship.

The syndrome has clinically been described thus: "Mucous colitis is a psychological disorder of the colon brought about through the action of the parasympathetic nervous system . . . the commonest source of parasympathetic overstimulation is . . . emotional tension . . . the three emotions, anxiety, guilt, and resentment, are those most commonly associated with tension in patients with mucous colitis"[175].

Since drug treatment in this condition must be directed toward either constipation or diarrhea, these symptoms will be discussed separately.

Constipation: Since it is likely that increased pressure ("spasm") in the sigmoid colon is responsible for constipation in these patients[8,79], resort to agents which would decrease this resistance and diminish local phasic activity seem indicated. *Anticholinergic* drugs of the quaternary amine variety, such as *propantheline* (15 to 30 mg. 3 or 4 times daily) which inhibit all gut activity by blocking acetylcholine at the neuromuscular junction and, to a much less extent at the ganglia[79], may accomplish this change. However, while discomfort may be relieved, evacuation usually will not occur, since these drugs also inactivate the propulsive activity of the right colon, necessary for normal bowel movements. The many advertised reports of the efficacy of these drugs in the irritable colon syndrome do not appear to be substantiated on extensive review of the literature[17]. *Laxative agents* are helpful and usually intermittent administration of one of the *mechanical* substances, the *bulk colloids* or a *saline* compound such as *milk of magnesia* will be sufficient. Some patients require stronger laxatives or the use of one of the irritant type of compounds: *anthraquinones, phenolphthalein, castor oil, resins, sulfur,* or *calomel.* While such treatment may be safely carried on for many years, it is well to remember that marked dependency often results, and occasionally, excessive use of these drugs leads to dehydration, electrolyte changes and even renal damage[136].

As discussed later, the doctor-patient relationship determines, to a great degree, the effectiveness of any laxative program.

Diarrhea: When diarrhea is the symptom to be treated, *anticholinergic drugs* again may be highly effective. *Propantheline,* particularly in the new long-acting form, two to three times daily (15 to 30 mg.) frequently diminishes the number of movements dramatically. This occurs most often when dosage is sufficient to produce side effects, such as dry mouth. This result is attributable to the inhibition of the gastro-colic reflex by quaternary amines and their "damping" effect upon the peristaltic "mass" action of the proximal colon[157]. The use of other anti-diarrheal drugs such as adsorbents, mucosal astringents, or hydrophilic substances does not seem worthwhile. *Opiates* may be useful; *paregoric* (Camphorated Tincture of Opium), 4 to 8 ml., 4 to 6 times daily, or *Deodorized Tincture of Opium,* 8 to 15 drops, or *codeine,* 16 to 32 mg., 2 to 4 times daily. However, they are used most wisely only over a short period to bring dramatic relief and thereby help establish an adequate doctor-patient relationship. The danger of prolonged usage is addiction.

Therapy for Emotional Stress in Irritable Colon Syndrome. While judicious use of a sedative such as *phenobarbital,* 15 to 30 mg. three times daily,

has been helpful in managing patients with this syndrome, some mention of the efficacy of the newer tranquilizing drugs should be made.

Included in this group are the *phenothiazine derivatives* (Thorazine, Promazine, and Compazine), *Rauwolfia derivatives* (Moderil, Serpasil), the *substituted alkanediols* (meprobamate, the *diphenylmethane derivatives* (Frequel, Atarax, Souvitil), and several miscellaneous compounds.

An extensive review of the pharmacologic properties of the various tranquilizing or ataractic drugs[173] is beyond the scope of this paper, but certain comments are necessary. These agents, singly and in combination with anticholinergic drugs, have been advocated strongly in the treatment of practically all of the gastrointestinal disorders. It is true that these drugs are potent psychopharmacologic agents and that patients may show some decrease in anxiety and hostility while being treated with these agents[77,173]; however, to date, no adequately controlled study of their usefulness in the therapy of the major complaints (diarrhea or constipation, or both) exists. It might be well to consider their properties and the data concerning their usefulness in the treatment of gastrointestinal disease.

All of these agents are capable of decreasing anxiety or manic states without markedly clouding the sensorium[77].

In addition, the phenothiazines[28] have an antiemetic action[112], potentiate barbiturates and narcotics[15,27,28] and block autonomic ganglia[41]. Distressing or harmful effects include postural hypotension[122,145], extra pyramidal and "tetanus-like" syndrome[80], cholestatic jaundice[38,174], bone marrow depression[72], skin reactions[72], seizure disorders[14,163] and photosensitivity[29,30a]. Meprobamate, in addition to its tranquilizing effect, causes peripheral muscle relaxation[46,63], and may be addicting[103].

It is clear, then, that these drugs must be prescribed for their specific psychopharmacologic effects and not for treatment for a specific gastrointestinal disorder. In patients with irritable colon or "functional dyspepsia," who are depressed, these drugs may increase the depression and thus further complicate the clinical course. In addition, it must be realized that to date there is no scientific evidence which demonstrates that these agents directly affect gastrointestinal disorders. It is probable, however, that these drugs, by allaying anxiety, will not only help to establish an adequate doctor-patient relationship, but also effectively combat the anxiety which underlies many gastrointestinal disorders. Casual usage or prescription in combination with other drugs as a substitute for these therapeutic aims is to be condemned.

2. CHRONIC INFLAMMATION OF THE SMALL AND LARGE BOWEL. *a. Ulcerative Colitis and Regional Enteritis.* Ulcerative colitis, a chronic inflammatory affliction of the colon, is characterized by remissions and exacerbations of rectal bleeding, diarrhea, cramping lower abdominal pain, fever and anorexia. Regional enteritis, a chronic granulomatous disease of the small intestine also is associated with diarrhea, fever and weight loss but gross bleeding is infrequent and the location of pain is periumbilical or right lower quadrant. Since the etiology of these diseases is unknown, therapy must be nonspecific.

In recent years much attention has been given the administration of either *adrenocorticotropic hormone* (ACTH) or *adrenocorticosteroids* (cortisone, hydrocortisone, prednisone, prednisolone, and others) in the treatment of idiopathic ulcerative colitis[54,90,91,170,180]. The rationale for the use of these substances in the management of ulcer-

ative colitis lies in their anti-inflammaory action and their effectiveness in relieving various associated symptoms, such as erythema nodosum, arthritis and iritis. Large numbers of such patients have been treated with these drugs, and the superiority of oral cortisone to placebo has been demonstrated adequately[53,170].

One of the largest series is that of Kirsner *et al.*, who treated 240 patients with ACTH or adrenal cortical steroids or both[90]. While initial responses, particularly to ACTH, were good in the vast majority of patients, permanent remission after one course was uncommon, occurring in about 16% only. Nevertheless, 75% of patients have benefited from repeated courses or continuous therapy. Symptoms were controlled in 60% of those under long-term (1 to 6 years) therapy.

Initial daily dosages of drugs recommended were: *ACTH*, aqueous, 40 to 60 units every 6 hours, intramuscularly; *cortisone*, 300 mg.; *hydrocortisone*, 200 mg.; and *prednisone*, 40 to 80 mg. per day in divided doses with tapering of 10 to 25% daily, depending upon the clinical response. Complications of long-term therapy included: infections, 43 patients; severe emotional disturbance, 40 patients (including 3 suicides); glycosuria, 30 patients; osteoporosis, 6 patients. Only 3 instances of peptic ulcer were noted; however, routine gastrointestinal roentgenologic examinations were not done in most patients. The incidence of perforation of the colon during administration of steroids or ACTH was not increased over that recorded in the pre-steroid era[90].

The use of ACTH is indicated in the treatment of the acute fulminant form of the disease in which the marked inflammatory process involves part of or the entire colon and penetrates all layers of the wall with attendant angiitis and thrombosis[158,171]. The patient is critically ill with high fever, protuberant abdomen, colonic dilatation, severe bleeding and prostration. Treatment for this acutely toxic state, which previously had a mortality of 20 to 40%, consists of replacement of blood, fluid, and electrolytes and the administration of *antibiotics* (penicillin, 600,000 units, and dihydrostreptomycin, 0.5 gm. twice daily, intramuscularly), in addition to aqueous *ACTH*, 30 to 40 units intravenously over an 8 to 12-hour period for 1 to 3 weeks, after which the drug usually may be given intramuscularly in gel form, 20 units twice daily. Dosage is reduced gradually as improvement ensues. It is well to give supplemental *potassium* (3 gm. daily by mouth or 40 mEq. per 1000 ml. of intravenous fluid) during the course of ACTH treatment. Of course, *vitamin B complex*, *vitamin K*, and *ascorbic acid* are included in the program.

Recently, reports of the use of corticosteroids locally by means of a "rectal drip" have appeared[151,168,169,172]. The basis for such therapy is the topical anti-inflammatory effect of these drugs. Patients with disease restricted to the rectum and recto-sigmoid, and at most the left colon, are most benefited. *Hydrocortisone hemisuccinate* (100 mg.) or *prednisolone* (50 to 75 mg.) in 100 to 125 ml. saline is instilled over a 60 to 90 minute period nightly, using a rectal catheter and regulation intravenous drip apparatus. In the majority of cases in whom the illness is mild or moderate, symptomatic relief, that is, decrease in the number of stools and cessation of bleeding is noted within 48 to 72 hours, and improvement of the proctoscopic picture parallels these changes. Remissions may last for several months, but repeat courses are usually necessary. Addition of antibiotics to the retention enema seems of no additional benefit, although it may

help in individual cases. It is of interest that only a small fraction of the administered steroid is absorbed from the lower colon, and therefore, systemic effects and complications are minimal.

The efficacy of *antibiotics* in the treatment of nonspecific inflammatory disease of the colon, except in the fulminant form, is not clear[18]. One can say, however, that such agents are not specific, but may reduce local tissue damage related to infection which in turn may be secondary to tissue ulceration and necrosis. In the usual case of ulcerative colitis, systemic broad spectrum drugs are withheld, principally because such agents as *tetracycline*, *oxytetracycline*, and others, may induce or increase diarrhea[51,92,93]. Further, prolonged use of "broad spectrum" antibiotics such as Neomycin may lead to problems of absorption, particularly of fat and fat soluble substances[74]. Some clinicians, who believe that tissue activity of bacteria is important in this disease, administer the nonabsorbable sulfonamides such as *salicylazosulfapyridine* (Azulfidine) 2 to 3 gm. every 4 to 6 hours. This is an inexpensive, relatively nontoxic antibacterial drug which apparently has an affinity for connective tissue and several authors report favorable results from its use [19,164]. Judgment of the efficacy of this agent in the usual patient with ulcerative colitis must be reserved, however, for several reasons: 1) No adequate control study with acceptable randomization, such as has been done in England with both oral[170] and intra-rectal[169] corticosteroids, has been carried out. 2) The natural history of patients with idiopathic ulcerative colitis, except for those in the fulminant phase, is unpredictable, but usually favorable in any one attack or exacerbation.

Experience with the use of *ACTH* and *adrenal steroids* in the treatment of *regional enteritis* is not so great as with ulcerative colitis. Scattered reports indicate that its effect may be gratifying in the acutely ill patient, but that maintenance dosages are often necessary and that, as with ulcerative colitis, response gradually may "wane" so that constant increments of the dose are required[29,66,88,109,134,147]. There is no indication as yet that long-term adrenocorticosteroid therapy significantly alters the course of the disease nor reduces the incidence of serious complications such as fistulization, abscess formation, and cicatrization with obstruction.

Something must be said here about the efficacy of *anticholinergic* drugs (*atropine* and the *quaternary amines*) and *opiates* in treatment of these diseases. While the former group will reduce gastrointestinal motor activity in normal patients, it is only rarely successful in the control of diarrhea and distress of these intestinal inflammatory conditions. Occasionally, *propantheline*, 30 mg., or an equivalent medication, at night may be helpful in reducing nocturnal movements and aftermeal distress due to a hyperactive gastro-colic reflex. In the face of conflicting claims of specificity and improved action, there is little evidence that there is any advantage of one quaternary amine over another. While *opiates*, either *paregoric* or *deodorized tincture of opium* may be efficacious, their usefulness is dependent upon short-term action, since tolerance and then addiction develop.

3. PEPTIC ULCERATION. Although there may be rare exceptions to the rule[69,120], peptic ulceration requires the action of an acid-pepsin combination on susceptible mucosa[142,148]. Because the factors determining mucosal susceptibility are as yet poorly understood, treatment is directed chiefly towards

reducing the volume, acidity and pepsin content of gastric juice. Our therapeutic armamentarium for achieving these ends includes a number of *antacids, anticholinergic, tranquilizing* and *sedative* drugs. In order to use these alone, or in combination, to the best effect, it is necessary to know the manner and degree in which a particular agent modifies the composition of gastric juice and what this modification costs in side effects, money and inconvenience to the patient.

In using *antacids*, one attempts to slow the peptic digestion of gastric and intestinal mucosa by elevating the pH of the gastric juice. For this purpose pH levels above 3.5 are probably desirable, since pepsin shows a maximal activity at pH 1 to 2 and will hydrolyze undenatured substrates only slightly at pH 3 to 4[37,56,130] (this, however, does not hold true for denatured proteins). From a therapeutic viewpoint, therefore, the objective is to maintain the gastric pH at approximately 3.5. The "maintaining" is all-important and requires adequate antacid dosage at frequent intervals over periods of weeks or months. The sporadic use of antacids cannot maintain any significant pH elevation and is of little value in the treatment of peptic ulceration.

In the selection of an antacid, such factors as duration of action, total acid-combining capacity, side effects, palatability and cost of the agent should be considered[9,26,89]. The duration of action for any particular antacid is dependent upon several factors: 1) its intrinsic chemical ability to neutralize a given amount of acid; 2) the composition of the gastric juice upon which it is acting; 3) the rate of gastric emptying; 4) the drug's solubility (a poorly soluble substance will tend to remain in the stomach for a longer period of time).

The principal side effects to be considered include the production of a systemic alkalosis by the more absorbable antacids, constipating or diarrheal effects and perhaps the production of renal calculi[65,82]. So-called "acid rebound" is also mentioned as a side effect associated with the use of some antacids[24,108], but the existence of such an effect is difficult to substantiate and its clinical significance is questionable[128, 129]. The binding of phosphorus by antacids containing aluminum is not a problem in patients on the usual ulcer diet. Although central nervous system depression is sometimes seen with the use of antacids containing magnesium, it is rarely significant unless renal insufficiency is also present[64].

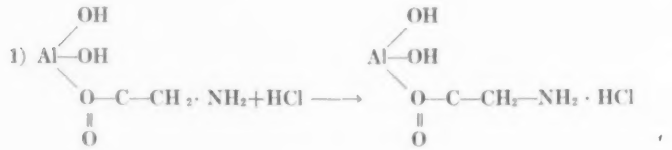
The following antacids are representative of those most in use at the present time: the aluminum and magnesium containing antacids, calcium bicarbonate, sodium bicarbonate, resins, sodium carboxymethylcellulose, and, to a small extent, mucin preparations. In discussing them individually, it will be seen that it is difficult to combine, in any single preparation, an effective and persistent neutralizing capacity with a freedom from side effects.

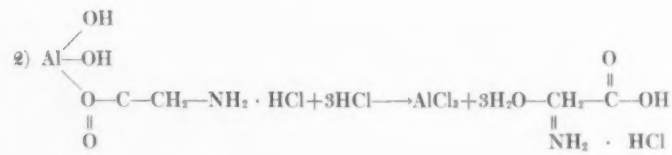
Aluminum hydroxide is representative of the aluminum-containing antacids[4,52,176]. Its action in the stomach it as follows: $Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$. There is little absorption of the poorly soluble, unneutralized material and little chloride loss (the aluminum chloride unites with the alkaline small bowel juices to form relatively insoluble basic aluminum salts). This drug, therefore, is a nonsystemic antacid which has essentially no effect on acid base balance. Aluminum ion has the additional useful property of inhibiting peptic activity to some extent, either by absorption or by direct effect on pepsin[96]. Orally administered aluminum hydroxide has no effect on the volume or acidity of juice

from isolated gastric pouches and has no significant effect on gastric motility[2,3,132]. Since constipation is the chief side effect, use of a preparation containing magnesium or addition of a laxative to the regimen is usually indicated. Of occasional clinical importance is the diminished absorption of the tetracycline drugs which are bound with aluminum ion[152].

Because aluminum chloride is an acid salt, it is not possible, even with large hourly doses of the hydroxide, to achieve a pH much above 2 to 3. Kirsner was able to maintain this range only with a 30 ml. per hour dosage of the hydroxide, alternating on the half hour with 90 ml. of a milk and cream mixture[85]. Although this does not represent an optimal neutralization of free hydrochloric acid, it would appear in most cases to be adequate for ulcer healing[26].

Di-hydroxyaluminumoacetate should be mentioned separately as an aluminum-containing antacid[137]. This represents an effort to combine the acid-neutralizing capacity of glycine with that of aluminum hydroxide. It neutralizes as follows:





Although there are some favorable reports[138], there is as yet inadequate clinical evaluation.

Of the *magnesium containing antacids, magnesium trisilicate* is perhaps representative[97,101,135]. In the stomach its reaction is as follows:

$$2MgO \cdot 3SiO_2 \cdot (H_2O)_x + 4HCl \rightarrow 2MgCl_2 + (H_2O)_{x+2}$$

The magnesium chloride reacts with bicarbonate in the intestinal tract to form magnesium carbonate, which is excreted, and sodium chloride which is reabsorbed. The silicon dioxide which is formed is thought by its coating action, to have some protective qualities[121]. There is little absorption of the unneutralized, poorly soluble base, and, therefore, no appreciable effect on acid base balance. Although its duration of action is prolonged, its neutralizing ability on a per weight basis is not as great as that of other antacids[81]. Its chief usefulness resides in its laxative properties which make it an advantageous drug to combine with more effective but constipating antacids.

Calcium carbonate is a highly effective antacid which is in neither of the above groups[85,107]. Its action in the stomach is as follows:

$$CaCO_3 + 2HCl \rightarrow CaCl_2 + H_2O + CO_2$$

In the small intestine the calcium chloride is converted to poorly soluble calcium salts and the chloride is reab-

sorbed with little fecal loss[83]. Since the unneutralized calcium carbonate is relatively insoluble, there is little effect on acid-base balance. It may rarely, however, produce a sufficient elevation in pH and serum calcium to depress renal function[49]. Although some calcium is absorbed, urinary calculi are not a common complication[89,94]. As with the aluminum-containing compounds, there may be marked constipation associated with the use of this agent and similar precautions are necessary.

With an hourly dosage of 2 to 4 gm., it should be possible to maintain a pH in the vicinity of 4.0[85], well within desired therapeutic limits. Because of this effectiveness, together with a relative freedom from side effects, it would seem to deserve wider usage[26].

Sodium bicarbonate represents a rapidly acting and highly effective antacid. It has, however, serious limitations because of its ability to produce a marked systemic alkalosis. The neutralizing reaction in the stomach is as follows:

$$NaHCO_3 + HCl \rightarrow CO_2 + H_2O + NaCl$$

The unneutralized bicarbonate is rapidly absorbed and, with prolonged use, is responsible for the systemic alkalosis. This alkalosis may be clinically significant and produce a variety of signs and symptoms including anorexia, nausea, headache, muscle aches and tetany[64]. It may seriously depress renal function[86] and, by decreasing the solubility of calcium phosphate, lead to the formation of renal calculi[9]. It is in connection with depressed renal function and high calcium intake that the so-called milk-alkali syndrome of Burnett may be seen with the various manifestation of hypercalcemia[30]. Because of this systemic action and the availability of other agents, sodium bicarbonate has little to recommend its use in the treatment of peptic ulcer.

The *polyamine resins* (Exorbin, Resinat) represent an interesting and promising class of antacids which act by binding hydrochloric acid in the stomach and releasing it in the alkaline medium of the small intestine[98]. This reaction can be represented by: $RX + HCl \rightarrow RX \cdot HCl$. The hydrochloric acid is then released in the intestine as: $2RX \cdot HCl + Na_2CO_3 \rightarrow 2RX + 2NaCl + H_2CO_3$.

The resins are nontoxic, insoluble, inert and without effect on acid base balance. In adequate dosage they are effective and rapidly acting neutralizers. To date, no significant side effects have been reported and constipation is not a problem[110,153]. The chief difficulty in their extensive use appears to be the dosage required for adequate pH control and the resultant cost of treatment.

Sodium carboxymethylcellulose is a salt of a polycarboxylic acid which forms a viscous solution in water. Although a weak antacid, it has few side effects and, because it appears to delay gastric emptying, may make a useful combination with other antacids[25,124,125].

The use of *gastric mucin* preparations in the treatment of peptic ulcer is based on some acid neutralizing and pepsin inhibiting properties and on its possible physiological protective coating for gastric mucosa[58,118]. It is a weak antacid and its mucosa protecting action has not been adequately demonstrated.

The *anticholinergic* drugs represent a second method of inhibiting the acid-pepsin combination. These vagal blocking drugs decrease the gastric and intestinal motility and the volume, pepsin content and acidity of the gastric juice[1,17,111,154]. Their effectiveness fre-

quently is limited by the associated side effects. These most commonly include blurring of the vision, dry mouth, tachycardia, dysuria or, in the presence of prostatic hypertrophy, urinary retention. Headache is sometimes annoying as is mild constipation, drowsiness, nervousness or increased irritability[11,62,87,119]. In susceptible individuals these drugs may precipitate an acute attack of glaucoma[17]. The tachycardia is an important consideration in the presence of gastrointestinal hemorrhage and the use of anticholinergic drugs in this situation will make a rising pulse difficult to evaluate. The decrease in gastric motility is undesirable in certain peptic ulcer patients, notably in those with partial or complete pyloric obstruction[40,98a].

The *anticholinergic* drugs may be divided into two classes: the *belladonna alkaloids* and their derivatives and the newer synthetic group consisting of various *quaternary ammonium compounds* and *tertiary amines*.

It is difficult to obtain clinical and experimental evidence sufficient to justify the selection of one anticholinergic drug, natural or synthetic, over the other[16,17]. As a general rule, it may be said that all anticholinergic drugs, in order to produce a satisfactory depression in acid secretion, must be taken in a dosage that approaches the limit of tolerance as far as side effects are concerned[87,115]. As stated in a recent review of anticholinergic drugs[17], "None of the anticholinergics have been proved to manifest unique specificity for any particular gastrointestinal organ, function or segment of the gastrointestinal tract, and there is no single anticholinergic of choice for any gastrointestinal ailment, unless it be atropine or belladonna because of their greatly lower cost."

Although in acceptable oral dosage (namely, to the point of side effects such as dry mouth) there is suppression of the basal, nocturnal, acid secretion, these drugs do not significantly affect the increased acid secretion in response to feeding or hypoglycemia[12,106,177]. During the day, therefore, anticholinergic therapy, in itself, can be of little use in raising pH to therapeutically useful levels. It may delay gastric emptying and prolong the action of simultaneously administered antacids[17]. The decrease in gastric and duodenal motility and spasm may also be a factor in relieving the pain of peptic ulceration although the complete mechanism is still not clear[70,127,10]. As yet, it has not been possible to demonstrate any increase in effectiveness by the use of prolonged acting tablets and capsules[17,20].

The exact role of anticholinergic drugs in the therapy of peptic ulcer is still uncertain. Controlled series have obtained comparable results with placebo substitutes[21,114,123]. There is, moreover, no evidence that long term administration alters the recurrence rate, incidence of complications or the need for eventual surgery[34,50,143,167].

Also of interest is the action of *sedatives*[89,116,126], *tranquilizers*[35,68,84], and *antihistamines*[13,78,146] on gastric secretion. Although usual maximal doses of *phenobarbital* and *sodium phenobarbital* were not found to produce a significant reduction in gastric secretion[116], Kirsner was able to show a decrease in acidity (7 of 15 patients) and volume (11 of 15 patients) of gastric juice by using relatively large and closely spaced intramuscular doses of sodium amytal (3 doses of 0.2 gm. at hourly intervals)[89]. Even in clinically applicable dosage, however, the often agitated and hyperirritable peptic ulcer patient may benefit from mild sedation. The effect of emotions on the gastric mucosa has been well demonstrated in the studies of Wolf and Wolff and

would appear pertinent[178]. In this respect, it is important to note that, as mentioned in the discussion of motility disorders of the bowel, there are no adequately controlled studies which show that tranquilizing drugs heal ulcers more rapidly or prevent complications or recurrences.

Reserpine, in usual oral dosage (approximately 1 mg. per day) has no significant effect on the volume and acidity of gastric juice. In larger, intramuscular dosage (1 to 2.5 mg.), however, there can be a marked increase in both of these factors[84]. Chlorpromazine has not been shown to have any effect on gastric secretion other than some lowering in volume output[68]. Although it would seem likely that the other *phenothiazine derivatives* would act in a similar manner, there is at present inadequate evidence for such conclusions.

Antihistaminics have been disappointing and most studies have shown no significant effect on gastric secretion in man[13,78,146].

4. DISEASES OF MALABSORPTION. During recent years it has become common practice to refer to all diseases and conditions resulting in impaired absorption from the small intestine as the malabsorption syndrome. Despite this general classification, therapy must be directed to the specific cause whenever possible. Although the purpose of this article is to discuss drug therapy, the other significant therapeutic measures also will be mentioned briefly.

Steatorrhea, a constant finding in the malabsorption syndrome, may lead to serious deficiencies of the fat soluble vitamins. For example, failure of vitamin D absorption, compounded by an abnormal loss of calcium in the stools, may result in severe osteomalacia. This defect in the bones is further aggravated by impaired protein utilization and osteoporosis. Deficient prothrombin production with hemorrhagic diathesis may result from inadequate absorption of vitamin K. Anemia, a frequent finding, may be due to iron deficiency, failure to absorb vitamin B_{12} or due to an abnormality in folic acid metabolism. In addition, there may be a marked weight loss and evidence of a vitamin B complex deficiency.

Despite recent advances, there remain many conditions for which management consists only of replacement therapy to correct these specific deficiencies which develop. Table 1 lists the dosage of those agents which are commonly used in the supportive treatment of diseases of malabsorption.

a. Primary malabsorption. Non-tropical sprue and *celiac disease*. During recent years, a remarkable advance in the treatment of these conditions has been made with recognition of the beneficial effect of the *gluten-gliadin-free diet*[57,60,141,144,159]. This is now the treatment of choice. Following institution of such dietotherapy, the steatorrhea and diarrhea subside within a short period and the various deficiencies are gradually corrected. The majority of the patients can be controlled by the diet alone. Drug replacement therapy is necessary only in those instances where one must correct a specific deficiency rapidly, for example, acute bleeding secondary to hypoprothrombinemia. The diet and representative recipes have been published in detail[102,160].

Although *corticosteroids* and *corticotropin* have been shown to improve the clinical status of patients with nontropical sprue[5,6,39,75,105,166], these agents do not seem to correct completely the steatorrhea[48,150,166], or biochemical abnormalities as does dietotherapy[5,57,150]. However, these drugs are indicated in 2 instances: 1) the treatment of the acutely ill patient; 2) the uncommon

situation where the disease (or patient) is "refractory" to the gluten-gliadin-free diet[5,6]. *Cortisone* (50 to 100 mg. daily) or *prednisone* (15 to 40 mg. daily) is effective in these instances[5,39,105,166]. Generally, it would seem unwise to administer these agents for a chronic condition in which the complications of the disease and the treatment are similar; namely, osteoporosis and impaired protein metabolism. However, in the critically ill patient with nontropical sprue, a rigorous therapeutic regimen consisting of *corticosteroids* or *corticotropin* (40 to 60 units daily), as well as intravenous salt-poor *albumin, vitamin K, calcium,* and blood transfusions is indicated. The corticosteroid treatment should be continued until the acute symptoms subside and the patient is taking a gluten-gliadin-free diet.

Remissions in *tropical sprue* have been noted with *antibiotics, hematinics,* administration of a low fat, high protein diet and migration to a temperate climate[61]. The gluten-gliadin-free diet has been shown to be ineffective in this condition[60]. *Folic acid, USP,* the therapeutic agent of choice, usually produces a complete symptomatic response[61,162]. Treatment should be started with 10 to 20 mg. daily and be reduced to a maintenance dose of 5 to 10 mg. after 10 to 14 days if definite improvement is noted. Addition of *broad spectrum antibiotic* drugs to the regimen would be justified if a prompt remission were not noted with folic acid. One to 2 gm. of *chlortetracycline* (Aureomycin) for 10 to 14 days appears adequate[59].

b. Secondary malabsorption. Gastric resection. Steatorrhea is occasionally of significance following a total gastrectomy and rarely after sub-total gastrectomy. The defect lies in improper mixing of the food with bile, owing to bypass of the duodenum, and the rapidity with which food reaches the small intestine. Fat absorption is increased by the ingestion of *ox-bile extract* (8 to 16 gm. daily in divided doses)[131]. *Pancreatic extracts* and *corticosteroids* have been ineffective[48]. A frequent feeding, high caloric diet with increased fat content is important to maintain good nutrition[23]. The patient with a total gastrectomy should be given 30 to 100 μg. of *vitamin* B_{12} intramuscularly monthly on a continuous basis. *Calcium, iron* and the *fat soluble vitamins A, D,* and *K,* may be added to this regimen as needed (Table 1).

Massive resection of the small intestine. It is important to remember that the amount of fat absorbed is proportional to the amount presented to the absorbing surface[149]. The fat intake, therefore, should be as high as tolerated. In severe cases, the outlined replacement therapy may have to be administered by the parenteral route. Because the distal ileum appears to be largely responsible for vitamin B_{12} absorption[22], extensive resection in this area should be followed by replacement therapy as in pernicious anemia or total gastrectomy. Iron deficiency anemia, a frequent finding, may not respond to oral *ferrous gluconate* (0.6 gm. three to four times daily) but may improve after use of the intramuscular *iron-dextran complex* (Imferon)[113]. Significant improvement has been reported in severely malnourished patients treated with *corticosteroids*[95]. These agents may be helpful if the usual supportive measures fail. Again one must be constantly alert to the complications of prolonged therapy. Stimulation of the appetite and improved sense of well-being may account for the beneficial effect as data do not conclusively show that corticosteroids improve absorption.

Obstruction of the biliary tree. Medical management of the patient with chronic biliary obstruction is a difficult

problem. Although *ox-bile* may increase absorption, it may intensify the pruritus. The diet should be high in protein without restriction of fat. The *fat soluble vitamins* and *calcium* should be provided in adequate amounts (Table 1). Anabolic hormones, *norethandrolone* (Nilevar, 30 to 60 mg. daily) or *methyl testosterone* (30 to 50 mg. daily), may improve protein synthesis as well as control the pruritus.

Pancreatic insufficiency. Treatment of this condition consists of therapy and prevention of recurrent acute attacks of pancreatitis. Among the available sources of digestive enzymes which improve absorption and decrease diarrhea are the various *commercial pan-*

TABLE 1.—REPLACEMENT THERAPY FOR MALABSORPTION STATES

I. FAT SOLUBLE VITAMINS

1. Vitamin A
   Oleovitamin A capsules, USP (25,000 units per capsule)100,000 to 200,000 units daily in severe deficiencies; maintenance: 25,000 to 50,000 units daily.
2. Vitamin D
   Synthetic Oleovitamin D, USP (10,000 USP units vitamin D/gram). 30,000 u. daily; increase dosage as necessary to raise serum calcium to normal. Dosage varies considerably depending on response as determined by level of serum calcium and urinary calcium.
3. Combination A and D Vitamins
   Concentrated oleovitamins A and D, USP (50,000 to 65,000 USP A units and 10,000 to 13,000 USP D units/gram) may be used rather than separate preparations.
4. Vitamin K
   Oral: Menadione, USP, 4 to 12 mg. daily. Vitamin K_1 tablets (Mephyton) 5 to 10 mg. daily.
   Intravenous: (bleeding episodes, acute situations). Vitamin K_1 (Mephyton) 50-mg. ampules. Administer slowly over 10 minute period. Repeat in 8 to 10 hours if prothrombin time has not returned to normal.

II. VITAMIN B-COMPLEX

Any multi-vitamin preparation which contains daily requirements (Thiamine 1.6 mg., riboflavin 1.8 mg. and niacin 20 mg.) use 2 or 3 tablets daily. Intramuscular preparations are available for severe deficiencies.

III. FOLIC ACID, USP (5 mg. tablets)

Dose: Initial: 10 to 20 mg. daily
Maintenance: 5 to 10 mg. daily

IV. VITAMIN B_{12} INJECTION, USP (15 μg./ml.)

Dose: Initial: 30 to 60 μg. daily for 2 to 3 weeks
Maintenance: 30 to 100 μg. monthly
If combined system disease is present, a more intensive program is indicated.

V. CALCIUM

Oral: Calcium gluconate (91 mg. Ca^{++}/gm.) 1 to 5 gm. 3 times daily.
Intravenous: Calcium gluconate injection, USP, 10% solution (9.1 mg. Ca^{++}/ml.) 10 to 30 ml. administered slowly intravenously depending upon response.

VI. IRON

Oral: Ferrous gluconate 0.6 gm. three times daily.
Intramuscular: (Imferon). Must be calculated according to severity of anemia. Detailed instructions accompany preparation.

VII. PANCREATIC SUPPLEMENTS

1. Pancreatin, USP, 6 to 18 gm. daily in divided doses.
2. Viokase, 4 to 12 gm. daily in divided doses.

Doses may be increased progressively until therapeutic effect is noted.

creatic extracts, Pancreatin, USP, or a preparation containing whole raw pancreas, *Viokase*[36]. To be effective, *Pancreatin* frequently must be used in a dosage of 10 to 20 gm. daily, an amount which often produces nausea and dyspepsia. *Viokase* (4 times the strength of Pancreatin, USP) is effective in a dosage range of 4 to 8 gm. daily. These preparations may be given in larger amounts if necessary, and are also more effective when given at regular intervals (6 times daily rather than when limited to mealtimes)[76].

Alteration of bacterial flora. This condition, which leads to defective absorption of vitamin B_{12} and fat[47,67], results from strictures, fistulae, blind loops or multiple diverticula of the small intestine. Whenever possible these abnormalities should be corrected surgically[32,155].

If surgical treatment is not feasible, the malabsorption may be corrected by the daily administration of 1 to 2 gm. of *broad spectrum antibiotics* (*chlortetracycline, tetracycline, oxytetracycline*) for 7 to 10 days[45,47,67,155]. *Neomycin* has been shown to be ineffective[47,67]. In this regard, it is important to note that broad spectrum antibiotics[117], especially *Neomycin*[74], occasionally produce steatorrhea in normal individuals.

Correction of the anemia is almost uniformly obtained with parenteral *vitamin* B_{12}. With restoration of normal vitamin B_{12} absorption following antibiotics, continuous parenteral administration of this vitamin is not necessary unless there is evidence of subacute combined degeneration of the spinal cord. Also, since malabsorption may recur, usually months or years later, periodic hematologic studies are indicated so that repeated courses of parenteral vitamin B_{12} and oral antibiotics may be given as indicated.

REFERENCES

(1) **Abbot, F. K., Mack, M.,** and **Wolf, S.:** Gastroenterology, **20**, 249, 1952. (2) **Adams, W. L.,** and **Clark, B. B.:** Am. J. Physiol., **141**, 255, 1944. (3) **Adams, W. L., Einsel, I. H.,** and **Myers, V. C.:** Am. J. Digest. Dis., **3**, 112, 1936. (4) Iidem: Ibid., **3**, 112, 1936–37. (5) **Adlersberg, D., Colcher, H.,** and **Wang, C. I.:** Ann. Int. Med., **38**, 554, 1953. (6) **Almy, T. P.:** Ibid., **34**, 1041, 1951. (7) Idem: Ann. New York Acad. Sci., **58**, 398, 1954. (8) **Almy, T. P., Kern, F. Jr.,** and **Tulin, M.:** Gastroenterology, **12**, 425, 1949. (9) **Almy, T. P.,** and **Steinberg, H.:** Drugs of Choice, p. 370, 1958–59. (10) **Asher, L. M.:** Gastroenterology, **18**, 21, 1951. (11) **Asher, L. M.,** and **Cohen, S.:** Ibid., **17**, 178, 1951. (12) **Ashby, D. W.,** and **Davis, A.:** Med. Illus., **7**, 865, 1953. (13) **Ashford, C. A., Heller, H.,** and **Smart, G. A.:** Brit. J. Pharmacol., **4**, 153, 1949. (14) **Ayd, F. J., Jr.,** *in* **Dorfman, W.,** Ed.: Transactions of the Fifth Annual Meeting of the Academy of Psychosomatic Medicine, New York, October, 1958. (15) **Azima, H.:** Canad. Med. Assn. J., **74**, 929, 1956.

(16) **Bachrach, W. H., Rowen, B. R., Halsted, J. A., Schapiro, H., Holmstrom, B. S.,** and **Price, P.:** Acta med. Scandinav. supplement 148, 288, 1954. (17) **Bachrach, W. H.:** Am. J. Digest. Dis., **3**, 743, 1958. (18) **Banks, B. N., Korelitz, B. I.,** and **Zetzel, L.:** Gastroenterology, **32**, 983, 1957. (19) **Bargen, J. A.:** Med. Clin. N. America, **33**, 935, 1949. (20) **Barowsky, H., Schwartz, S. A.,** and **Lister, J.:** Am. J. Gastroenterol., **27**, 156, 1957. (21) **Bechgaard, P., Bang, H. O., Nielsen, A. L.,** and **Tobiassen, E.:** Am. J. Digest. Dis., **21**, 38, 1954. (22) **Booth, C. C.,** and **Mollin, D. L.:** Lancet, **1**, 18, 1959. (23) **Brain, R. H.,** and **Stammers, F. A.:** Ibid., **1**, 1137, 1951. (24) **Breuhaus, H. C., Akre, O. K.,** and **Eyerly, J. B.:** Gastroenterology, **16**, 172, 1950. (25) **Brick, I. B.:** Am. J. Digest. Dis., **16**, 315, 1949. (26) **Brody, M.,** and **Bachrach, W. H.:** Ibid., **4**, 435, 1959. (27) **Bronner, A.:** Am. J. Psychotherapy, **10**, 460, 1956. (28) **Brooks, G. W.:** New England J. Med., **254**, 1119, 1956. (29) **Brown, C. H.,** and **Daffner, J. E.:** Ann. Int. Med., **49**, 595, 1958. (30) **Burnett, C. H., Commons, R. R., Albright, F.,** and **Howard, J. E.:** New England

J. Med., **240**, 787, 1949. (**31**) **Butin, J. W., Olsen, A. M., Moersch, H. J.,** and **Code, C. F.:** Gastroenterology, **23**, 278, 1953.

(32) **Cameron, D. G., Watson G. M.,** and **Witts, L. J.:** Blood, **4**, 793, 1949. (**33**) **Casten, G. G.,** and **Boucek, R. J.:** J. Am. Med. Assn., **166**, 319, 1958. (**34**) **Cayer, D.:** Am. J. Digest. Dis., N.S., **1**, 301, 1956. (**35**) **Clark, M. L.,** and **Schneider, E. M.:** Gastroenterology, **29**, 877, 1955. (**36**) **Clay, W. A., Frank, D. W.,** and **Logan, V. W.:** Ibid., **26**, 198, 1954. (**37**) **Christensen, L. K.:** Arch. Biochem. and Biophysiol., **57**, 163, 1955. (**38**) **Cohen, J. M.,** and **Archer, J. D.:** J. Am. Med. Assn., **159**, 99, 1955. (**39**) **Colcher, H.,** and **Adlersberg, D.:** The Malabsorption Syndrome (Symposium). New York: Grune & Stratton, p. 213, 1957. (**40**) **Colbert, J. R.:** J. Oklahoma Med. Assn., **46**, 149, 1953. (**41**) **Courvoisier, S., Fournel, J., Ducrot, R., Kilsky, M.,** and **Koetschet, P.:** Arch. Int. Pharmacodyn., **92**, 305, 1953. (**42**) **Creamer, B.,** and **Code, C. F.:** Gastroenterologia, **86**, 763, 1956. (**43**) **Creamer, B., Fyke, F. E., Jr., Code, C. F.,** and **Olsen, A. M.:** Clin. Res. Proc., **4**, 130, 1956. (**44**) **Cross, F. S.:** Surgery, **31**, 647, 1952.

(45) **Dick, A. P.:** Brit. Med. J., **1**, 145, 1955. (**48**) **Dickel, A. H., Wood, J. A.,** and **Dixon, H. H.:** Ann. New York Acad. Sci., **67**, 780, 1957. (**47**) **Doscherholmen, A.,** and **Hagen, P. S.:** J. Lab. & Clin. Med., **44**, 790, 1954. (**48**) **Drenick, E. J., Hvolboll, E.,** and **Halsted, J. A.:** New England J. Med., **253**, 303, 1955. (**49**) **DuFault, F. X., Jr.,** and **Tobias, G. J.:** Am. J. Med., **16**, 231, 1954.

(50) **Echerverria Martinez, E.:** Rev. espan. enferm. ap. digest., **11**, 29, 1952. (**51**) Editorial: New England J. Med., **249**, 37, 1953. (**52**) **Einsel, I. H., Adams, W. L.,** and **Myers, V. C.:** Am. J. Digest. Dis., **1**, 513, 1934. (**53**) **Elliott, J. M.,** and **Carbones, J. V.:** Gastroenterology, **33**, 423, 1957. (**54**) **Elliott, J. M.,** and **Giansiracura, J. E.:** New England J. Med., **250**, 969, 1954. (**55**) **Evans, J. A.:** A.M.A. Arch. Dermat., **79**, 64, 1959.

(56) **Feller, W.,** and **Imamoglu, K.:** Surg. Forum. **8**, 205, 1957. (**57**) **Finlay, J. M.,** and **Wrightman, K. J. R.:** Ann. Int. Med., **45**, 191, 1956. (**58**) **Fogelson, S. J.:** A.M.A. Arch. Int. Med., **55**, 7, 1935. (**59**) **French, J. M., Gaddie, R.,** and **Smith, N. M.:** Quart. J. Med., **25**, 333, 1956. (**60**) **French, J. M., Hawkins, C. F.,** and **Smith, N.:** Ibid., **26**, 481, 1957.

(61) **Gardner, F. H.:** New England J. Med., **258**, 791, 1958. (**62**) **Gelfand, M. L.:** New York J. Med., **52**, 1917, 1952. (**63**) **Gillette, H. E.:** Internat. Rec. Med., **169**, 453, 1956. (**64**) **Goodman, L. S.,** and **Gilman, A.:** The Pharmacological Basis of Therapeutics, 2nd ed. New York: Macmillan Company, p. 1034, 1955. (**65**) **Grace, W. J.,** and **Barr, D. P.:** Am. J. Med., **4**, 331, 1948. (**66**) **Gray, S. J., Reifenstein, R. W., Benson, J. A., Jr.,** and **Young, J. C. G.:** A.M.A. Arch. Int. Med., **87**, 646, 1951.

(67) **Halsted, J. A., Lewis, P. M.,** and **Gasster, M.:** Am. J. Med., **20**, 42, 1956. (**68**) **Haverback, B. J., Stevenson, T. D., Sjoerdsma, A.,** and **Terry, L. L.:** Am. J. Med. Sci., **230**, 601, 1955. (**69**) **Heffernan, E. W., Kiefer, E. D.,** and **Tracey, M. L.:** New England J. Med., **241**. 604, 1949. (**70**) **Hightower, N. C.,** and **Gambill, E. E.:** Gastroenterology, **23**, 244, 1953. (**71**) **Hochman, R., Jeffries, G.,** and **Sleisenger, M. H.:** Unpublished data. (**72**) **Hodges, H. H.,** and **Lazerte, G. D.:** J. Am. Med. Assn., **158**, 114, 1955.

(73) **Ingelfinger, F. J., Kramer, P.,** and **Sanchez, G. C.:** Am. J. Med. Sci., **228**, 417, 1954.

(74) **Jacobson, E. D., Chodos, R. B., Prior, J. T.,** and **Faloon, W. W.:** Clin. Res., **7**, 260, 1959. (**75**) **Jones, C. M.:** Acta med. Scandinav., **146**, 25, 1953. (**76**) **Jordon, P. H.,** and **Grossman, M.:** Gastroenterology, **36**, 447, 1959.

(77) **Kaplan, H. S.:** New York State J. Med., **59**, 2871, 1959. (**78**) **Kay, A. W., Scott, L. D. W.,** and **Smith, W. E.:** Glasgow Med. J., **28**, 145, 1947. (**79**) **Kern, F., Jr., Almy, T. P.,** and **Stolk, N. J.:** Gastroenterology, **17**, 198, 1951. (**80**) **Kinross-Wright, V.:** Ann. New York Acad. Sci., **61**, 174, 1955. (**81**) **Kirsner, J. B.:** Am. J. Digest. Dis., **8**, 53, 1941. (**82**) Idem: Ibid., **8**, 160, 1941. (**83**) Idem: J. Clin. Invest., **22**, 47, 1943. (**84**) **Kirsner, J. B.,** and **Ford, H.:** A.M.A. Arch. Int. Med., **99**, 390, 1957. (**85**) **Kirsner, J. B.,** and **Palmer, W. L.:** Am. J. Digest. Dis., **7**, 85, 1940. (**86**) Iidem: Arch. Int. Med., **69**, 789, 1942. (**87**) Iidem: J. Am. Med. Assn., **151**, 798, 1953. (**88**) **Kirsner, J. B., Palmer, W. L.,** and **Klotz, A. P.:** Gastroenterology, **20**, 229, 1952. (**89**) **Kirsner, J. B., Palmer, W. L., Levine, E.,** and **Klotz, A. P.:** Ann. Int. Med., **35**, 785, 1951. (**90**) **Kirsner, J. B., Palmer, W. L., Spencer, J. A., Bicks, R. O.,** and **Johnson, C. F.:** Ibid., **50**, 891, 1959. (**91**) **Kirsner, J. B., Sklar, M.,** and

Palmer, W. L.: Am. J. Med., **22**, 264, 1957. (**92**) **Kleckner, M. S., Jr., Bargen, J. A., and Baggenstoss, A. H.:** Gastroenterology, **21**, 212, 1952. (**93**) **Klotz, A. P., Palmer, W. L., and Kirsner, J. B.:** Ibid., **25**, 44, 1953. (**94**) **Knapp, E. L.:** J. Clin. Invest., **26**, 182, 1947. (**95**) **Kogan, E., Schapira, A., Janowitz, and Adlersberg, D.:** Am. J. Digest. Dis., **3**, 844, 1958. (**96**) **Komarov, S. A., and Komarov, O.:** Ibid,. **7**, 166, 1940. (**97**) **Kraemer, M.:** Ibid., **8**, 56, 1941. (**98**) **Kraemer, M., and Siegal, L. H.:** A.M.A. Arch. Surg., **56**, 318, 1948. (**98a**) **Kramer, P.:** New England J. Med., **251**, 600, 1954. (**99**) **Kramer, P., and Ingelfinger, F. J.:** Am. J. Med., **7**, 168, 1949. (**100**) Iidem: Gastroenterology, **19**, 242, 1951. (**101**) **Kurtz, P.:** J. Lab. & Clin. Med., **24**, 1015, 1939.

(**102**) **Law, D. H., Benson, G. D., and Sleisenger, M. H.:** G. P., in press. (**103**) **Lemere, F.:** A.M.A. Arch. Neurol. & Psychiat., **76**, 205, 1956. (**104**) **Lendrum, F. D.:** Arch. Int. Med., **59**, 474, 1937. (**105**) **Lepore, M. J.:** Am. J. Med., **25**, 381, 1958. (**106**) **Levine, E., Kirsner, J. B., and Palmer, W. L.:** Gastroenterology, **21**, 339, 1952. (**107**) **Loevenhart, A. S., and Crandall, L. A.:** J. Am. Med. Assn., **88**, 1557, 1927. (**108**) **Lopusniak, M. A., and Berk, J. E.:** Gastroenterology, **11**, 891, 1948.

(**109**) **Machella, T. E., and Hollan, O. R.:** Am. J. Med. Sci., **221**, 501, 1951. (**110**) **Martin, G. J., and Wilkinson, J.:** Gastroenterology, **6**, 315, 1948. (**111**) **Mattman, P. E., and Strutner, L.:** Am. J. Digest. Dis., **20**, 126, 1953. (**112**) **Mayer, J. H.:** Med. Clin. N. America, **41**, 405, 1957. (**113**) **McCurdy, P. R., Rath, C. E., and Meerfrebs, G. E.:** New England J. Med., **257**, 1147, 1957. (**114**) **McDonough, F. E., and Hammond, J. B.:** Med. Clin. N. America, **38**, 459, 1954. (**115**) **McKenna, R. D., Smith, S. A., and Wyse, D. N.:** Gastroenterology, **26**, 476, 1954. (**116**) **Merendino, K.:** Ibid., **10**, 504, 1948. (**117**) **Merliss, R. R., and Hoffman, A.:** New England J. Med., **245**, 328, 1951. (**118**) **Mitchell, T. C.:** J. Physiol., **73**, 421, 1931. (**119**) **Mody, M. V., and Keeney, A. H.:** J. Am. Med. Assn., **159**, 1113, 1955. (**120**) **Morlock, C. G., and Ratke, H. V.:** Gastroenterology, **13**, 241, 1949. (**121**) **Mutch, N.:** Brit. Med. J., **2**, 735, 1937. (**122**) **Moyer, J. H., Kent, B., Knight, R., Morris, G., Huggins, R., and Handley, C.:** Am. J. Med. Sci., **227**, 283, 1954.

(**123**) **Narcussen, J. M., and Solem, J. H.:** Nord. Med., **44**, 1282, 1953. (**142**) **Necheles, H., Kroll, H., Bralow, S. P., and Spellberg, M. A.:** Am. J. Digest. Dis., **18**, 1, 1951. (**125**) Iidem: Ibid., **18**, 7, 1951. (**126**) **Noble, C. L.:** Canad. Med. Assn. J., **60**, 55, 1949.

(**127**) **Palmer, W. L., and Kirsner, J. B.:** Tr. Assn. Am. Phys., **65**, 303, 1952. (**128**) **Periera-Lima, J., and Hollander, F.:** Gastroenterology, **37**, 145, 1959. (**129**) Iidem: Ibid., **37**, 154, 1959. (**130**) **Perry, J. F., Jr., Yonehiro, E. G., Ya, P. M., Root, H. D., and Wagensteen, O. H.:** Proc. Soc. Exper. Biol. & Med., **72**, 237, 1956. (**131**) **Polak, M., and Pontes, J.:** Gastroenterology, **30**, 489, 1956.

(**132**) **Quigley, J. P., Einsel, I. H., and Meschan, I.:** J. Lab. & Clin. Med., **24**, 485, 1939.

(**133**) **Rake, G. W.:** Guy's Hosp. Rep., **77**, 141, 1927. (**134**) **Redish, W. H.:** Gastroenterology, **18**, 179, 1951. (**135**) **Reid, C. G.:** Am. J. Digest. Dis., **6**, 267, 1939. (**136**) **Relman, A. S., and Schwartz, W. B.:** New England J. Med., **255**, 195, 1956. (**137**) **Reuling, J., Rossieu, A. X., and Wolgel, M. I.:** Rev. Gastroenterol., **16**, 856, 1949. (**138**) **Rider, J. A., Gibbs, J. O., Swader, J., Van Der Reis, L., and Lee, J.:** Am. J. Digest. Dis., **1**, 287, 1956. (**139**) **Rodnan G. P., Black, R. L., Bollet, J. A., and Bunim, J. J.:** Ann. Int. Med., **44**, 16, 1956. (**140**) **Rosenthal, F. D.:** Gastroenterology, **32**, 332, 1957. (**141**) **Ross, C. A. C., Frazer, A. C., French, J. M., Gerrard, J. W., Sammons, H. G., and Smellie, J. M.:** Lancet, **1**, 1087, 1955. (**142**) **Roth, J. A., and Bockus, H. L.:** Gastroenterology, **15**, 374, 1950. (**143**) **Ruffin, J. M., Texter, E. C., Carter, D. D., and Baylin, G. J.:** J. Am. Med. Assn., **153**, 1159, 1953. (**144**) **Ruffin, J. M., Carter, D. D., Johnston, D. H., and Baylin, G. J.:** New England J. Med., **250**, 281, 1954.

(**145**) **Sainz, A. A.:** Psychopharmacology, Pub. 42, Am. Assn. Adv. Sci., 1956. (**146**) **Sangsta, W., Grossman, M. I., and Icy, A. C.:** Gastroenterology, **6**, 436, 1946. (**147**) **Sauer, W. G., Brown, P. W., and Dearing, W. H.:** Ibid., **22**, 550, 1952. (**148**) **Schwartz, K.:** Beitr. z. klin. Chir., **67**, 96, 1916. (**149**) **Schwartz, M. K., Medwid, A., Roberts, K. E., Sleisenger, M., and Randal, H. T.:** Surg. Forum, **6**, 1956. (**150**) **Schwartz, M. H., Sleisenger, M. H., Pert, J. H., Roberts, K. E., Randall, H. T., and Almy, T. P.:** Gastroenterology, **32**, 232, 1957. (**151**) **Schwartz, R. D., Cohn, G. L., Bondy, P. K., Brodoff, M., Supton, G. V., Spiro, H. M.:** Proc. Soc.

Exper. Biol. & Med., **97**, 648, 1958. (**152**) **Seed, J. C.,** and **Wilson, C. E.:** Bull. Johns Hopkins Hosp., **86**, 415, 1950. (**153**) **Segal, H. L., Hodge, H., Watson, J. S.,** and **Scott, W. J. M.:** Gastroenterology, **4**, 484, 1945. (**154**) **Silver, H. M., Pucci, H.,** and **Almy, T. P.:** New England J. Med., **252**, 520, 1955. (**155**) **Siurala, M.,** and **Kaipainen, W. J.:** Acta med. Scandinav., **147**, 197, 1953. (**156**) **Sleisenger, M. H.:** *In* Long Term Illness, **Wohl, M.,** Editor. Philadelphia: W. B. Saunders Co., p. 263, 1959. (**157**) **Sleisenger, M. H., Eisenbud, M.,** and **Almy, T. P.:** Gastroenterology, **27**, 829, 1954. (**158**) **Sleisenger, M. H., Law, D. H.,** and **Almy, T. P.:** Med. Clin. N. America, **41**, 775, 1957. (**159**) **Sleisenger, M. H., Law, D. H., Kowlessar, O. D., Pert, J. H.,** and **Almy, T. P.:** Tr. Assn. Am. Phys., **71**, 100, 1958. (**160**) **Sleisenger, M. H., Rynbergen, J. H., Pert, J. H.,** and **Almy, T. P.:** J. Am. Diet Assn., **33**, 1137, 1957. (**161**) **Sleisenger, M. H., Steinberg, H.,** and **Almy, T. P.:** Gastroenterology, **25**, 333, 1953. (**162**) **Spies, T. D.:** Experiences with Folic Acid. Chicago: Year Book Publishers, 1947. (**163**) **Stewart, L. F.: EEG** with Folic Acid. Chicago: Year Book Publishers, 1947. (**163**) **Stewart, L. F.:** EEG Clin. Neurophysiol., **9**, 427, 1957. (**164**) **Svartz, N.:** Gastroenterology, **26**, 26, 1954. (**165**) **Swenson, O.:** New England J. Med., **260**, 972, 1959.

(166) **Taylor, A. B., Wollaeger, E. E.,** and **Comfort, M. W.:** Gastroenterology, **20**, 203, 1952. (**167**) **Texter, E. C., Jr., Legerton, C. W., Ruffin, J. M., Atwater, J. S., Cayer, D., Cheney, F. D., Jackson, R. A.,** and **Oren, B. G.:** South. Med. J., **46**, 1062, 1953. (**168**) **Truelove, S. C.:** Brit. Med. J., **1**, 1437, 1957. (**169**) Idem: Ibid., **2**, 1072, 1958. (**170**) **Truelove, S. C.,** and **Witts, L. J.:** Ibid., **2**, 1041, 1957.

(171) **Warren, S.,** and **Sommers, S.:** Am. J. Path., **25**, 657, 1949. (**172**) **Watkinson,, G.:** Brit. Med. J., **2**, 1077, 1958. (**173**) **Werner, G.:** Am. J. Med. Sci., **237**, 631, 1959. (**174**) **Werther, J. L.,** and **Korelitz, B. I.:** Am. J Med., **22**, 351, 1957. (**175**) **B. V., Cobb, S.,** and **Jones, C. M.:** Psychosom. Med., Monographic series, No. 1, 1939. (**176**) **Wilkinson, S. A.,** and **Comanduras, P. D.:** New England J. Med., **223**, 972, 1940. (**177**) **Winkelstein, A.:** Gastroenterology, **20**, 464, 1952. (**178**) **Wolf, S.,** and **Wolff, H. G.:** Human Gastric Function. New York: Oxford University Press, 1947.

(179) **Zarafonetis, C. J. D.:** Ann. Int. Med., **50**, 343, 1959. (**180**) **Zetzel, L.:** New England J. Med., **257**, 1120, 1957.

BOOK REVIEWS AND NOTICES

DISEASES OF METABOLISM: DETAILED METHODS OF DIAGNOSIS AND TREATMENT. Edited by GARFIELD G. DUNCAN, M.D., Professor of Medicine, University of Pennsylvania. 4th ed. Pp. 1104; 343 ills. Philadelphia: W. B. Saunders Company, 1959. Price, $18.50.

THIS fourth edition of what has become a standard reference for metabolic diseases has been completely rewritten with the help of many new contributors. The formats of earlier editions have been preserved with encyclopedic discussions of protein, carbohydrate and fat metabolism engaging the first three chapters prepared by Salter, Levine and Gurin respectively. The section on mineral metabolism is devoted largely to calcium, phosphorus, parathyroid gland interrelationships, and metabolic bone disease with some curtailment of the presentations on other equally important mineral factors. The excellent section on water balance, electrolytes and renal function previously written by the late Dr. Peters has been revised as one of the outstanding contributions in the book by Welt. There are nearly 300 pages devoted to various aspects of nutrition, including Vitamins and Avitaminosis by Spies and coworkers, Undernutrition by Keys, and Obesity by Strang. Integration of current investigative work with established clinical concepts is effectively achieved in these sections as elsewhere in the text. The editor has drawn upon his vast experience in the field of diabetes to prepare a superlative chapter on the management of this disease and its complications. Other sections of the book written by eminent authorities deal with Disease of the Kidney, the Thyroid, Juvenile Diabetes, Diabetes Inspidus, Hypoglycemia, Porphyrins, Gout and Glycogen Storage Disease.

This is a book to be included in the library of every practicing physician. It is designed to provide insight into new and changing concepts upon which clinical applications can be based. The extensive bibliographies, appendix and index are representative of the care with which the book has been prepared.

C.S.

THE ANATOMY OF THE NERVOUS SYSTEM. By S. W. RANSON, M.D., Late Professor of Neurology, Northwestern University, Chicago. Revised by S. L. CLARK, M.D., PH.D., Professor of Anatomy, Vanderbilt University, Nashville. 10th ed. Pp. 622; 434 ills., 10 in color. Philadelphia and London: W. B. Saunders Co., 1959. Price, $9.50.

THIS text continues to be the most widely used on anatomy of the nervous system as testified by the publication of this 10th edition. By the inclusion of functional aspects, its value to the students as well as to the clinician and research worker has been greatly enhanced. The terminology is chiefly that adopted by the International Anatomical Nomenclature Committee in 1955. Recent advances, as for instance the studies of Larsell on the cerebellum, have been included so that the book remains up-to-date and can be highly recommended.

E.S.

L'ARTHROGRAPHIE OPAQUE DU GENOU. By PAUL FICAT, Electro-radiologist and Assistant in Surgery of Hospitals in Paris. Pp. 244; 139 ills. Paris: Masson et Cie, 1957. Price, 3.800 fr.

THIS book is based on a review of 600 cases of opaque arthrographies of the knee. It contains six main chapters describing the history, anatomy, technique, normal arthrograms, abnormal arthrograms, and finally the author describes diagnostic signs of meniscal and cartilaginous pathology. A number of good references (59) are given at the end of this book. The author describes the limitations of this technique as well as its indications. The reviewer feels that the book is useful to radiologists and orthopedic surgeons and the technique is of value in selected cases.

A.B-P.

INDUSTRIAL CARCINOGENS. By ROBERT E. ECKHARDT, M.D., PH.D., F.A.C.P., Director, Medical Research Division, Esso Research and Engineering Company, Linden, N.J., Associate Clinical Professor of Industrial Medicine, New York University, Instructor in Medicine, Cornell University. Pp. 164; 22 ills. New York: Grune & Stratton, Inc., 1959. Price, $6.50.

THIS volume is one of a series, *Modern Monographs in Industrial Medicine,* edited by Anthony J. Lanza, M.D., who supplied the Foreword to this work. The author provides a concise review of modern knowledge of industrial carcinogens and related cancers;

their origins, relation to occupation and means of prevention. The subject matter of this monograph is timely and important in today's complex and ever-growing industrial world.

Dr. Eckhardt divides his study into 6 chapters: 1) Historical, 2) Experimental carcinogens, 3) Occupational cancers, 4) Protective programs, 5) Medico-legal considerations, and 6) A look into the future. An accurate text, appropriate illustrations, selected bibliography at the end of each chapter, and concluding index make this book a valuable addition in the field of occupational medicine.

F.R.

DIE WIRBELSAULE IN FORSHUNG UND PRAXIS, BAND 9. SCHMERZ: TRAUMA:BEGUTACHTUNG. Edited by DR. MED. HERBERT JUNGHANNS, Oldenburg. Authors: F. DITTMAR, H. JUNGHANNS, A. LOB, E. PICHLER, L. ZUKSCHWERDT U.A. Pp. 96; 40 ills. Stuttgart: Hippokrates Verlag, 1959. Price, DM 21.50.

THIS volume contains a collection of papers most of which were presented at an orthopedic meeting at Freudenstadt (Germany) in 1957. Drs. Junghans, Zukschwerdt and Lob discuss legal aspects, Pichler and Bues, headache and neckache, and Dittmar neurological segmented diagnosis of trauma of the spine. Köhler describes his experiences with diagnosis and treatment of vertebral decompensation due to sport injury, while Kohlrausche presents results of his roentgenologic studies of various extension methods used in the treatment of injury of lumbar discs. The articles are well illustrated. They are a valuable addition to this series of books on the vertebral column.

W.E.

THE FAMILY MEDICAL ENCYCLOPEDIA. BY JUSTUS J. SCHIFFERES, PH.D., Director, Health Education Council; illustrated by LOUISE BUSH, PH.D., Pp. 617. Boston: Little, Brown and Company, 1959. Price, $4.95.

THIS book, compiled by a former Managing Editor of *Modern Medicine*, affords a nontechnical source of family health information. Comprehensive in scope, it combines an alphabetical health encyclopedia, an elementary medical dictionary and a concise manual of first aid. Numerous lucid black-and-white drawings illustrate the text.

Reviewed by an advisory board of 8 prominent physicians, this volume is readable, up-to-date and broad in scope. It is recommended to laymen as a simple, yet accurate guide in health matters.

F.R.

A HANDBOOK OF MEDICAL HYPNOSIS. BY GORDON AMBROSE, L.M.S.S.A., Consulting Psychiatrist, Marriage Guidance Council and GEORGE NEWBOLD, M.B., B.S., M.R.C.S., M.M.S.A., D.R.C.O.G., D.C.H., Late Obstetrician and Gynecologist, Orsett Lodge Hospital. 2nd ed. Pp. 276 Baltimore: The Williams & Wilkins Company (Exclusive U.S. agents), 1958. Price, $6.75.

IN a clear concise style, the authors present their view of hypnotherapy and its role in the general practice of medicine. They speak with a conviction of their successful management of medical and surgical problems. The reader may be intrigued with the wide range of illnesses for which hypnotherapy is employed. It was used with a degree of success in multiple sclerosis, hypertension, peptic ulcer, various pediatric and dermatological disorders. A bibliography and an index is included.

The book will appeal to those persons interested in the use of hypnosis in medicine.

M.B.

THE MANAGEMENT OF FRACTURES AND DISLOCATIONS. AN ATLAS: VOLUMES I AND II. BY ANTHONY F. DEPALMA, M.D., Professor of Orthopedic Surgery, Jefferson Medical College. Pp. 960; 1927 ills. Philadelphia: W. B. Saunders Co., 1959. Price, $35.00 per set.

THIS new two-volume text is also new in format. The written word is less than the illustrations. The latter are well done pencil drawings depicting the various types of fractures and also drawings to show how the reduction is performed. Since the illustrations are lucid, the written aspect can be less: the author has done this by simply outlining the remarks necessary. This plan also obtains for the section under "Principles." In most cases the methods of treatment follow along conventional lines used by most fracture men. When open surgery is required the method advised is in many cases that devised by the author. It follows then that this text will find great use among students and internes and general practitioners. However, for the specialist-to-be it will have to be supplemented with other texts to obtain a broader scope of the subject. Where to seek this the text does not help for the bibliography is conspicuous by its absence.

The physical aspect of these two books is excellent. A.S.

PLAYING FOR LIFE, BILLY TALBERT'S STORY. BY WILLIAM F. TALBERT WITH JOHN SHARNIK. Pp. 310; 12 ills. Boston: Little, Brown and Company, 1959. Price, $4.00.

THIS is an interesting book concerned with the problems of a young diabetic patient who rose to the challenge of his disease to become one of the foremost stars in the tennis world. The personal recountal of the problems involved in self-care of diabetes under these conditions will provide profitable and enjoyable reading for all diabetic patients and for physicians who are involved in their management. Those who have heard Billy address lay diabetic groups know of his enthusiasm for inspiring and helping others with the disease at considerable personal sacrifice of time and expense. C.S.

THE PHYSIOPATHOLOGY OF CANCER. Edited by FREDDY HOMBERGER, M.D., Research Professor of Medicine, Tufts University School of Medicine. By 32 AUTHORS. 2nd ed. Pp. 1180; 189 ills. New York: Paul B. Hoeber, Inc., 1959. Price, $33.00.

THIS is an enlarged and revised edition of a book first published in 1953 and edited at that time by Freddy Homberger, M.D., and William Fishman, Ph.D. It presents recent and collected information in review chapters, each with an extensive bibliography, in fulfillment of its stated purpose of providing up-to-date knowledge of the total picture of cancer in a single volume.

The twenty-eight chapters, each by an outstanding worker in the area reviewed, are arranged in four sections to form sub-units devoted to the biology of cancer, the chemistry and physics of cancer, clinical investigations in cancer research, and the application of basic scientific knowledge to diagnosis and chemical and radiation treatment of cancer.

Of special interest in the section on the biology of cancer is a chapter on genetics of neoplasia by Clarence Cook Little, Sc.D., which presents the genetic approach to cancer, from the broad concepts of growth potential, cell division rate, organization of cells, the balance of physiologic and reparative organization and functioning of an organism.

In the other sections, equally fundamental and informative statements of broad biologic principles characterize the writings. This is a thoroughly enjoyable book which serves at once both as informative review and provocative statement of fundamental biologic principles in the field of cancer.

The only significant criticism to be made of this book is that its price, $33.00, seems unnecessarily high. H.W.

NEOPLASTIC DISEASE AT VARIOUS SITES. VOLUME II, TUMOURS OF THE BLADDER. Edited by DAVID M. WALLACE, O.B.E., M.S., F.R.C.S., University of London. Pp. 351; 202 ills. Edinburgh and London: E. & S. Livingstone, Ltd. (The Williams & Wilkins Co., Baltimore, exclusive U.S. Agents), 1959. Price, $11.50.

THIS book is the second volume of a proposed thirteen volume set on neoplasms at individual sites. Bladder tumors are extensively discussed from the point of view of the statistician, industrial or experimental organic chemist, pathologist, radiotherapist, physician, and surgeon. The monograph is divided into seven sections, the first four devoted to statistics, the industrial risks, the etiology and biochemistry of bladder tumors, and the pathology. The last three sections are entirely clinical beginning with the clinical assessment, followed by the methods of surgical treatment, and finishing with an analysis of the treatment.

Analyses of statistics reveal that in spite of all modern advances in prevention and treatment the mortality from bladder tumors is rising.

There is one chapter devoted exclusively to the biochemical changes that occur following uretero-colic anastamosis.

The volume is well written, the photomicrographs are excellent, and the tables quite clear. It is highly recommended to the clinician and to the basic science worker who will be able to obtain a comprehensive review of the current clinical management. L.K.

PLAGUE FIGHTER: AN AUTOBIOGRAPHY OF A MODERN CHINESE PHYSICIAN. BY WU LIEN-TEH, M.A., M.D.(CANTAB.). Pp. 640; 20 ills. Cambridge, England: W. Heffer and Sons, Ltd., 1959. Price, 30 s. net.

THE author was a fighter from childhood. His father, a native of Canton, China, migrated south to Penang at the age of sixteen. He was gifted with brawn and brains and became wealthy as an inventor and jewelry salesman. He married a Chinese lady who

gave birth to eleven children, five sons and six daughters. Dr. Wu was the fourth son and grew up under competitive conditions which made him enjoy fighting. He had most of his education and training at Cambridge with one year of special study at Johns Hopkins. Dr. Wu was then one of the few Chinese doctors well educated in modern medicine.

The first four chapters of his book relate in detail his search for the etiology of plague and its transmission. Anyone interested in contagious diseases should enjoy reading these chapters. The rest of the book gives an account of Dr. Wu's many movements to improve conditions in China and South Asia. It contains a complete history of the Wu family, which should be of special interest to them and their friends.

Dr. Wu Lien-Teh has been and is one of the great men of China and will long be honored by the Chinese. J.M.

Trifluoperazine: Clinical and Pharmacological Aspects. Twenty-five Original Reports with an introduction by HENRY BRILL, M.D., Assistant Commissioner, New York State Department of Mental Hygiene. Pp. 219; 3 ills. Philadelphia: Lea & Febiger, 1958. Price, $3.50.

TRIFLUOPERAZINE (Stelazine) is the newest of the phenothiazine drugs to be released. It is a very powerful agent whose use demands considerable care. This monograph contains 23 clinical papers and 2 papers describing pharmacologic and toxicity studies in various psychiatric conditions. H.D.

Ego Psychology and the Problem of Adaptation. By HEINZ HARTMANN, Member of the Faculty of the New York Psychoanalytic Institute. Translated by DAVID RAPAPORT. Pp. 121. New York: International Universities Press, Inc., 1958. Price, $3.00.

THIS work represents a systematic attempt to establish within the framework of a psychoanalytic ego psychology the groundwork for a theory of human behavior in general, normal as well as abnormal.

In this essay there is a discussion of concepts such as the undifferentiated phase, the conflict free ego sphere, conflict free ego development, and primary and secondary autonomy. The role of endowment, the inborn ego apparatuses and their adaptive nature, and other concepts crucial to psychoanalysis are considered in this work.

A bibliography pertinent to the subject of adaptation is included. This book is mandatory reading for all students of psychoanalysis. M.B.

The Year Book of Medicine (1958–1959 Series). Edited by PAUL B. BEESON, M.D., CARL MUSCHENHEIM, M.D., WILLIAM B. CASTLE, M.D., TINSLEY R. HARRISON, M.D., FRANZ J. INGELFINGER, M.D., AND PHILIP K. BONDY, M.D. Pp. 782; 123 ills. Chicago: The Year Book Publishers, Inc., 1958. Price, $7.50.

THIS is the 1958–59 edition of the now familiar series of abstract reviews which cover a large portion of the literature in internal medicine which appeared during the preceding year. As before, the areas included are: Infections; Chest; Blood and Blood-Forming Organs; Heart, Blood Vessels and Kidney; Digestive System; and Metabolism.

Although brief, the abstracts are generally adequate and give the essential points to be gained from the original papers. The reader will find this a competent and valuable survey of the material reviewed. C.Z.

Chemical Transformations by Microorganisms. By FRANK H. STODOLA, Agricultural Research Service, U.S. Department of Agriculture, Peoria, Ill. Pp. 134. New York: John Wiley & Sons, Inc., 1958. Price, $4.25.

THIS book is based on the second series of the E. R. Squibb Lectures on Chemistry of Microbial Products. The lectures cover the chemical anatomy of bacteria with special reference to *Mycobacterium tuberculosis*, review the diversified organic type reactions carried out by microorganisms and give examples of their remarkable synthetic activities. Of special interest are a summary of recent chemical studies on bacteria grown *in vivo*, illustrations of the application of microorganisms in the synthesis of amino acids, oligosaccharides and steroids and a review of the work on gibberellins.

Dr. Stodola, an organic chemist with experience and insight in microbiology, has made important contributions in the topics presented and speaks with first hand knowledge. The presentation is comprehensive, highly readable, and not interrupted by technical descriptions of chemical procedures which instead are outlined in flow sheets. M.F.

Convulsive Disorders of Children. By DORA HSI-CHIH CHAO, RALPH DRUCKMAN AND PETER KELLAWAY, Baylor University College of Medicine. Pp. 151; 25 ills. Philadelphia: W. B. Saunders Company, 1958. Price, $6.00.

THIS is a revision of a manual used by residents at the Blue Bird Circle Children's Clinic, Houston, Texas. It presents in readable fashion both the clinical management of the patients with seizures, and the pathological physiology and anatomy of epilepsy.

The chapter "The Investigation of Seizure Patients" should be of particular benefit to practitioners who handle this problem infrequently;

a "Drug Table," extending over two pages, is the most complete and precise which this reviewer has seen. Unfortunately, a chapter "Epilepsy of Adult Life" is included and seems incompatible with the authors' objectives.

This book will be useful to interns and residents, and to practitioners who infrequently handle the epileptic child. R.G.

Abnormal Uterine Bleeding. Edited by JOHN I. BREWER, M.D., and *Special Diagnostic Aids.* Edited by C. PAUL HODGKINSON, M.D. Pp. 295; 93 ills. Vol. I. No. 3. New York: Paul B. Hoeber, Inc., 1958. Price, $18.00 per year.

THE third issue of the quarterly book series, Clinical Obstetrics and Gynecology, is devoted to reviews of Abnormal Uterine Bleeding (edited by John I. Brewer) and Diagnostic Aids (edited by C. Paul Hodgkinson). Among the special diagnostic aids considered are new methods for recognizing early malignant uterine and ovarian tumors, culdoscopy, roentgenographic studies of the pelvic bones and soft tissues, methods for evaluating bladder function, sex diagnosis, blood incompatibility and coagulation defects. The symposium on uterine bleeding is opened by a long and comprehensive discussion of etiology and continues with shorter papers concerning diagnostic methods and bleeding during the various age periods and finally one on the emotional aspects of bleeding.

The material is directed toward practitioners rather than investigators and usually represents the ideas and conclusions formulated by each author from his own special work in the field. Practical methods of diagnosis and treatment, many of which can be carried out in an office or a small hospital, are presented. The bibliographies are limited but the references are usually to important articles.

This publication should prove valuable to students, residents and practitioners, both specialists and family doctors. J.W.

Initiation Mathematique a la Physique Medicale et a la Biologie. BY JULIEN GUELFI. Pp. 220; 94 ills. Paris: Masson et Cie, 1958. Price, 4.000 fr.

Annales Universitatis Mariae Curie-Sklodowska, Sectio D, Medicine, Vol. XII, 1957. Pp. 364; illustrated. Uniwersytet Marii Curie-Sklodowskiej, 1957.

TWENTY-FOUR papers on various subjects published by the press of the Universitatis Mariae Curie-Sklodowska.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Published Monthly. Illustrated.

Subscription price: 1 year $10.00; 2 years $18.00.

(One year subscription to Canada, $10.50; all other countries $12.00)

All foreign subscriptions payable in advance in United States dollars.

Business Correspondence: Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, Pa.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence should be sent to the Editor:

DR. RICHARD A. KERN, Temple University School of Medicine, Philadelphia 40, Pa.

Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side only, of good quality paper and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle.

ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. Line drawings and charts should be prepared with black India ink. Special arrangements can be made for printing color plates, elaborate tables or an excessive number of illustrations.

REFERENCES should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 REPRINTS will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100. An order form showing cost of reprints is sent with proof. Individual reprints can usually be obtained by writing directly to the author.